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Research Article

Ultrasound Shear Wave Elastography in Differentiating Benign and Malignant Ovarian Masses

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Received: April 01, 2026; **Published:** May 07, 2026

Abstract

Purpose: To study the role of ultrasound shear wave elastography in differentiating benign and malignant ovarian masses.

Materials and Methods: Fifty-six patients with complex ovarian masses on ultrasound were included. Transabdominal shear wave elastography (SWE) was done, and the solid component of the mass was selected. The mean elasticity values (kPa) and mean velocity values (m/sec) were compared between benign and malignant ovarian masses, keeping histopathology the gold standard.

Results: The elasticity parameters of benign and malignant ovarian masses differed statistically. The mean elasticity (kPa) evaluation demonstrated a cut-off value of 18.92 kPa in differentiating benign and malignant ovarian masses, with an average mean elasticity of 9.32 kPa in benign and 46.27 kPa in malignant masses. Similarly, mean velocity demonstrated a cut-off value of 2.46 m/s for differentiating the same, with an average mean velocity of 1.56 m/s in benign masses and 3.50 m/s in malignant masses. The p-value was < 0.001 for mean elasticity values (kPa) and < 0.001 for mean velocity values (m/sec).

Conclusion: Ultrasound shear wave elastography contributes significantly to the differentiation of benign and malignant ovarian masses.

Keywords: *Ultrasound; Shear Wave Elastography; Benign; Malignant; Ovarian Masses; Histopathology*

Introduction

Ovarian masses are one of the most common gynaecological problems encountered in daily clinical practice. Ovarian cancer is the sixth most common cancer globally and the third most common cancer in India. It is the most common cause of cancer-related deaths resulting from gynaecological malignancies, with an overall 5-year survival rate of less than 50% [1-4]. It accounts for 3.34% of cancer deaths in India [5].

Most patients exhibit non-specific symptoms in the early stages, leading to a delay in the diagnosis. This significantly affects the treatment outcomes and long-term survival. If detected in stage 1, the 5-year survival rate is 90%; however, in stage III/IV, it is 28% [4]. Therefore, an early distinction between benign and malignant ovarian masses is crucial. Various imaging techniques like ultrasound (US), Colour Doppler, computed tomography (CT), Magnetic resonance imaging (MRI) and Positron emission tomography-computed tomography scan (PET CT) have been widely used in the preoperative diagnosis of ovarian tumours.

Ovarian masses represent a broad spectrum, from benign to malignant. Benign masses comprise Cystadenomas, Brenner tumors, fibrothecomas, Mature cystic teratomas, Struma ovarii, and sclerosing stromal tumors. Malignant masses include serous and mucinous cystadenocarcinomas, endometrioid carcinomas, clear cell carcinomas, dysgerminomas, granulosa cell tumours, immature teratomas, endodermal sinus tumours, choriocarcinomas, and metastases. These masses should be accurately characterised for optimal management of the patients.

The current gold standard for diagnosing ovarian masses is histopathology (HPE), but it is invasive, and hence, there is a need for non-invasive, accurate preoperative radiological diagnosis. Ultrasound (US) is the primary imaging modality, and Colour Doppler can be added to analyse blood flow patterns. However, it is operator dependent, has limited spatial resolution and faces technical constraints like body habitus and bowel gas.

The International Ovarian Tumour Analysis Group (IOTA) has developed simple US-based rules for differentiating benign and malignant masses. Five simple rules each were selected to predict malignancy (M rules) and benign tumour (B rules). However, 20% of cases show equivocal imaging features, and other diagnostic modalities are necessary to categorise them. Thus, the IOTA rules have limited applicability and cannot categorise every mass [6]. The Ovarian-Adnexal Reporting and Data System (O-RADS) US risk stratification and management system applies the standardised reporting tool for Ultrasound based on the 2018 published O-RADS US working group lexicon. It stratifies into six categories (O-RADS 0-5), incorporating the range from normal to high risk of malignancy [7]. However, the lesion may be indeterminate on ultrasound and require further assessment.

MRI can differentiate benign and malignant masses with an overall accuracy of 88% to 93% [8]. Contrast-enhanced MRI also provides similar accuracy (84 - 93%) [9]. However, limited availability, high cost, and longer scan times are some of its limitations. A CT scan is the primary imaging modality for staging ovarian cancers. Still, routine use of CT to differentiate benign and malignant ovarian masses is not recommended due to the risk of radiation. Hence, the need of the hour is a non-invasive, widely accessible, radiation-free, and cost-effective imaging modality.

Sonoelastography can play an important role in imaging and characterising ovarian masses. It is an innovative technique, and the principle is to utilise the altered elasticity of soft tissues due to some pathology. There are two methods: Strain elastography, which is a qualitative or semiquantitative technique using internal or external compression stimuli, and Shear wave, which is a quantitative technique using ultrasound-generated travelling shear wave stimuli [10]. Sonoelastography would be a cost and time-saving technique.

Aim of the Study

Our study aims to determine the role of transabdominal shear wave sonoelastography (SWE) in differentiating benign and malignant ovarian masses, considering HPE as the gold standard. To date, minimal research has been done on the role of elastography in gynaecological imaging, and this is the first study evaluating the role of shear wave elastography in ovarian masses. The present study aims to establish cut-off values of Shear-wave quantitative parameters to differentiate benign and malignant ovarian masses and also their association, if any, with the histological grade of malignant masses.

Materials and Methods

This observational cross-sectional study was conducted at the Department of Radiodiagnosis in collaboration with the Departments of Obstetrics and Gynaecology and Pathology over 18 months from April 2023 to September 2024. The study protocol was approved by the Institutional Ethical Committee of Vardhman Mahavir Medical College and Safdarjung Hospital (IEC/VMMC/Thesis/2023-CC287). Written informed consent was obtained from all patients.

The study comprised 56 patients diagnosed with complex ovarian masses on ultrasound. Simple cystic ovarian lesions, masses not adequately visualised or included within 8 cm of the SWE scan area, either due to the patient's body habitus or technical issues, and those who did not undergo surgery or HPE were excluded. Transabdominal SWE was performed on an Affinity 70G US machine with an elastography-compatible C (5-2) convex transducer. The largest solid component of each ovarian lesion was assessed to measure tissue stiffness, with the quantitative parameters being mean elasticity (kPa), median range (kPa), and mean velocity (m/s). These results were used to establish cut-off values for distinguishing benign and malignant lesions. Histopathological examination or image-guided biopsy was used to confirm the final diagnosis.

Statistical analysis

Data was coded and recorded in the MS Excel spreadsheet program. For data analysis, SPSS v21 (IBM Corp.) was used. The association between two categorical variables were examined using the Chi-square test. Where the expected frequency in the contingency table was less than 5 for more than 25% of the cells, Fisher's Exact test was employed as an alternative. The linear correlation between two continuous variables was assessed using Pearson's correlation for normally distributed data and Spearman's correlation for non-normally distributed data. To assess its diagnostic performance, the investigation under study had its sensitivity, specificity, PPV, NPV, and diagnostic accuracy calculated. Statistical significance was kept at $p < 0.05$.

Results

The study comprised 56 ovarian masses, including 37 malignant (66%) and 19 benign (34%), with final diagnoses confirmed by HPE. The mean age of participants was 40.3 ± 14.3 years, with no significant age difference between the benign (38.3 years) and malignant (41.3 years) groups. Among the 56 masses, 33 were epithelial tumours, including 23 serous cystadenocarcinomas, 3 mucinous cystadenocarcinomas, 3 serous cystadenomas, 2 clear cell carcinomas, 1 Brenner's tumour, and 1 mucinous cystadenoma. The remaining masses included other malignant and benign types, such as Krukenberg tumours, endometriomas, and mature cystic teratomas. The study found a higher-than-expected incidence of malignancy (66%), which may be attributed to the tertiary care and referral nature of our institute. Additionally, many benign tumours were managed conservatively and were not operated on.

Shear wave sonoelastography (SWE) was used to assess tissue stiffness in all complex ovarian masses. The quantitative parameters measured were mean elasticity (kPa), median range (kPa), and mean velocity (m/s). The mean elasticity (kPa) was significantly associated with ORADS, Mean Velocity (m/s), HPE, and tumour grade (Table 1). The average mean elasticity of benign masses was 9.32kPa, and 46.27kPa in malignant masses; p-value < 0.001. A significant cut-off of 18.92 kPa was established to differentiate benign and malignant ovarian masses, with a sensitivity of 78.4% and specificity of 89.5% (Table 2 and figure 1). The strength of Association (Point-Biserial Correlation) was 0.41 (large effect size).

Parameters	Median Range (kPa)	p value
USG ORADS* **		<0.001[2]
ORADS 2	4.86 ± 4.37	
ORADS 3	18.89 ± 23.99	
ORADS 4	17.33 ± 12.12	
ORADS 5	49.60 ± 51.86	
Mean Velocity (m/s)* **	Correlation Coefficient (rho) = 0.92	<0.001[1]
Histopathology Diagnosis* **		<0.001[2]

Brenners Tumor	9.95 ± 0	
Clear Cell Carcinoma	21.45 ± 11.03	
Dysgerminoma	7.15 ± 0	
Endometrioma	3.35 ± 1.03	
Granulosa Cell Tumour	28.55 ± 8.70	
Immature Teratoma	3.94 ± 0	
Krukenberg Tumour	98.37 ± 69.80	
Mature Cystic Teratoma	6.02 ± 5.80	
Metastatic Adenocarcinoma	24.90 ± 0	
Mucinous Cystadenocarcinoma	15.60 ± 16.98	
Mucinous Cystadenoma	2.59 ± 0	
Serous Cystadenocarcinoma	44.24 ± 41.12	
Serous Cystadenoma	10.13 ± 3.82	
Tubo-Ovarian Abscess (TB)	13.73 ± 0	
Histopathology Impression* **		<0.001[3]
Benign	8.63 ± 8.53	
Malignant	46.85 ± 49.01	
Tumour Grade* **		0.001[3]
Low Grade	13.41 ± 10.56	
High Grade	58.27 ± 53.78	

Table 1: *Association between mean elasticity (kPa) and other parameters.*

****Significant at p < 0.05, 1: Spearman Correlation, 2: Kruskal-Wallis Test, 3: Wilcoxon-Mann-Whitney U Test.*

Variable	AUROC	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Mean Elasticity (kPa) (Cutoff: 18.92 by ROC)	0.876	78.4% (62-90)	89.5% (67-99)	93.5% (79-99)	68.0% (46-85)	82.1% (70-91)
Median Range (kPa) (Cutoff: 17 by ROC)	0.878	78.4% (62-90)	89.5% (67-99)	93.5% (79-99)	68.0% (46-85)	82.1% (70-91)
Mean Velocity (m/s) (Cutoff: 2.46 by ROC)	0.859	75.7% (59-88)	89.5% (67-99)	93.3% (78-99)	65.4% (44-83)	80.4% (68-90)

Table 2: *Performance of SWE parameters for predicting histopathology: Malignant vs benign.*

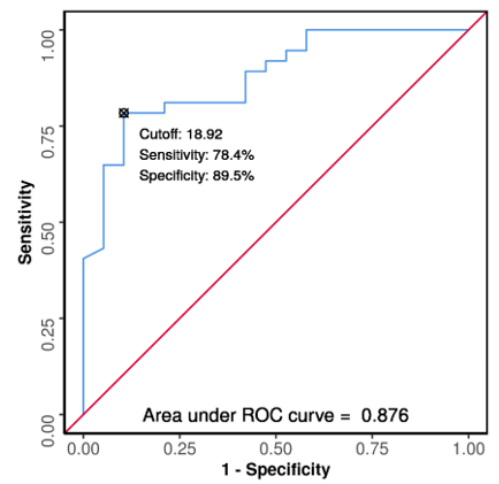

Figure 1: *ROC curve analysis I: Diagnostic performance of mean elasticity (kPa) in predicting histopathology: malignant vs benign (n = 56).*

The median range elasticity (kPa) was also significantly associated with ORADS, Mean Velocity (m/s), HPE, and tumour grade. There was a significant difference between the benign and malignant groups (W = 86.000, p = <0.001), with a value of 8.63 kPa in benign masses and 46.85 kPa in malignant. The strength of association (Point-Biserial Correlation) was 0.42 (large effect size), similar to the mean elasticity.

The mean velocity (m/s) was significantly associated with ORADS, mean elasticity (kPa), HPE, and tumour grade (Table 3). An average mean velocity of 1.56 m/s was observed in benign masses and 3.50 m/s in malignant masses; p-value < 0.001. Further, a significant cut-off of 2.46 m/s (< 0.001) was established, with 75.7% sensitivity and 89.5% specificity in differentiating benign and malignant ovarian masses (Table 2 and figure 2). The strength of association (Point-Biserial Correlation) was 0.52 (large effect size). The highest mean velocity was found in Krukenberg tumours (4.6 m/s). Interestingly, mean elasticity and mean velocity showed a progressive increase from ORADS 2 to ORADS 5 (Table 1 and 3). Few endometriomas, having a complex pseudo-solid appearance due to the presence of varying stages of blood products, also exhibited mean elasticity and velocity values within the benign range.

Parameters	**Mean Velocity (m/s)**	**p value**
USG ORADS* **		<0.001[2]
ORADS 2	1.22 ± 0.55	
ORADS 3	2.16 ± 1.41	
ORADS 4	1.93 ± 0.83	
ORADS 5	3.69 ± 1.81	
Mean Elasticity (kPa)* **	Correlation Coefficient (rho) = 0.92	<0.001[1]
Median Range (kPa)* **	Correlation Coefficient (rho) = 0.92	<0.001[1]

Histopathology Diagnosis* **		0.001[2]
Brenner's Tumour	1.81 ± 0	
Clear Cell Carcinoma	2.68 ± 0.76	
Dysgerminoma	1.57 ± 0	
Endometrioma	1.05 ± 0.20	
Granulosa Cell Tumour	3.32 ± 0.06	
Immature Teratoma	3.02 ± 0	
Krukenberg Tumour	5.51 ± 1.82	
Mature Cystic Teratoma	1.33 ± 0.72	
Metastatic Adenocarcinoma	2.91 ± 0	
Mucinous Cystadenocarcinoma	2.28 ± 1.44	
Mucinous Cystadenoma	0.91 ± 0	
Serous Cystadenocarcinoma	3.33 ± 1.66	
Serous Cystadenoma	1.86 ± 0.40	
Tubo-Ovarian Abscess (TB)	1.74 ± 0	
Histopathology Impression* **		<0.001[3]
Benign	1.56 ± 0.80	
Malignant	3.50 ± 1.80	
Tumour Grade* **		0.001[3]
Low Grade	1.76 ± 0.48	
High Grade	3.96 ± 1.87	

Table 3: *Association between mean velocity (m/s) and other parameters.*

****Significant at p < 0.05, 1: Spearman Correlation, 2: Kruskal-Wallis Test, 3: Wilcoxon-Mann-Whitney U Test.*

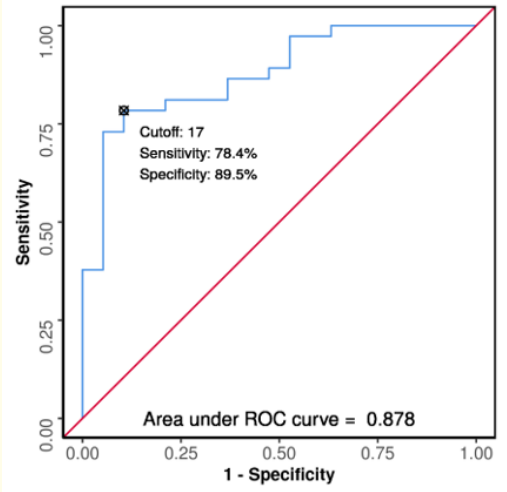

Figure 2: *ROC curve analysis II: Diagnostic performance of mean velocity (m/s) in predicting histopathology: malignant vs benign (n = 56).*

The secondary objective of the present study was to assess whether transabdominal SWE could predict the aggressiveness or grade of malignant ovarian masses. Histopathological grading was done for 34 malignant masses, 26 being high-grade and 8 being low-grade tumours, revealing significant differences in their kPa and m/s values. A mean elasticity cut-off of ≥ 24.5 kPa showed 81% sensitivity and 88% specificity for predicting high-grade tumours, with an AUROC of 0.877. Mean velocity > 2.91 m/s showed a sensitivity of 77% and specificity of 100% for predicting high-grade malignancy, with an AUROC of 0.882.

Discussion

It is essential to characterise complex ovarian masses and predict the likelihood of malignancy preoperatively, as it becomes crucial in determining the surgical strategy or feasibility of conservative patient management. Sonoelastography is a novel technique in gynaecological imaging and can play an important role in characterising ovarian masses. The present study is the first of its kind, evaluating the role of shear wave elastography in ovarian masses. Thus, the results have been compared with other similar studies sharing the same guiding principle and framework, done for breast or thyroid masses.

The present study comprised 56 ovarian masses, including 37 malignant and 19 benign masses. There was no statistically significant difference between the benign and malignant groups of tumours in terms of age. Patients with benign tumours had a mean age (yrs.) of 38.3, and those with malignant tumours had a mean age of 41.3. This was comparable to a study by Sharadha S., *et al*. where the mean age (yrs) for benign tumours was 39 and malignant tumours were 41. In their study, serous cystadenomas were the most common benign neoplastic mass. Whereas, in the present study, mature cystic teratoma was the most common benign mass (Figure 3). However, serous cystadenocarcinomas (Figure 4) were found to be the most common malignant masses in both studies [11].

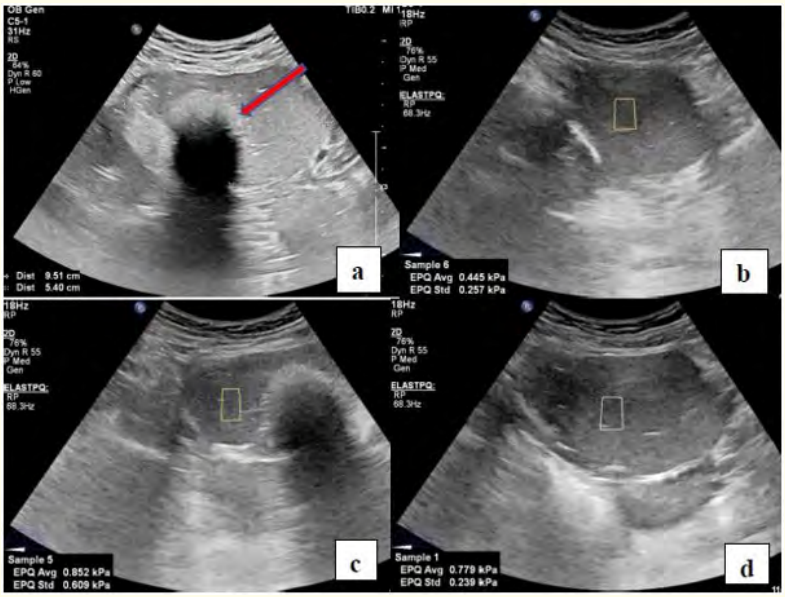

Figure 3: *US elastography benign ovarian mass: 26-year-old female with mild abdominal pain and irregular menstrual cycles. (a) On TAS, the right adnexal solid mass lesion with a hyperechoic area with posterior acoustic shadowing is likely a Rokitansky protuberance (red arrow). (b-d) Shear wave elastography with ROI in the solid areas. Mean elasticity 0.58; Mean velocity 0.43 HPE - Mature Cystic Teratoma.*

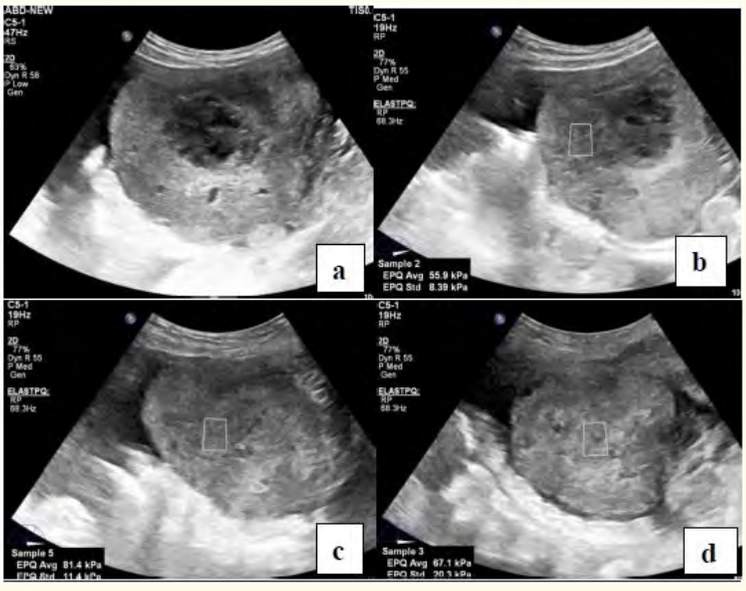

Figure 4: *US elastography malignant ovarian mass: A 34-year-old female with lethargy and gastrointestinal symptoms like bloating and loss of appetite. (a) On TAS, a large abdominopelvic predominantly solid mass with central necrosis. (b-d) Shear wave elastography with ROIs placed in the solid areas. Mean elasticity 31.18; Mean velocity 3.22 m/s. HPE - clear cell carcinoma.*

SWE was performed on all the complex ovarian masses, and the mean elasticity (kPa), median range (kPa) and mean velocity (m/s) were calculated. The evaluation of mean elasticity (kPa) demonstrated a cut-off value of 18.92 kPa to be statistically significant (< 0.001) in differentiating between benign and malignant ovarian masses with 78.4% sensitivity and 89.5% specificity. The median of mean elasticity was the highest in the Krukenberg tumour, with a value of 66.53 kPa (Figure 5). Cebi Olgun D., *et al*. did a similar study on 115 breast masses. The elasticity values were significantly higher in the malignant group than in the benign group, and the cut-off value for mean elasticity was 45.7 kPa, with a sensitivity of 96% and specificity of 95% [12].

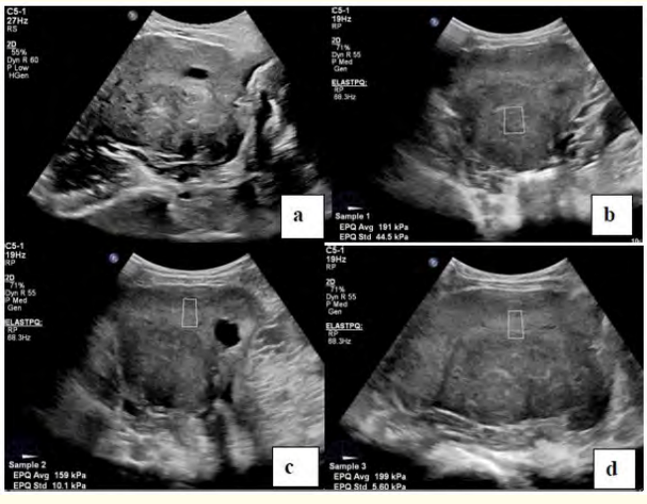

Figure 5: *US elastography metastatic ovarian mass: A 27-year-old with abdominal pain for two months. (a) On TAS, a large abdominopelvic solid cystic mass was seen in the right adnexa. (b-d) Shear wave elastography with ROIs kept in the solid areas. Mean elasticity 201.2 kPa; Mean velocity 8.17 m/s. HPE - metastatic signet ring cell adenocarcinoma with gastrointestinal primary.*

Similarly, shear wave sonoelastography was used to characterise thyroid nodules in children and adolescents by Hazem M., *et al*. Seventy-two thyroid nodules in patients (11 to 19 years) were studied, and it was found that malignant nodules had higher shear wave elasticity values. They obtained a mean elasticity cut-off value of 42.2 kPa for differentiating benign and malignant thyroid nodules with 85.71% sensitivity, 94.83% specificity and 93.06% accuracy [13].

In the present study, the mean velocity (m/s) demonstrated a cut-off value of 2.46 m/s for differentiating benign and malignant ovarian masses with 75.7% sensitivity, 89.5% specificity, and 80.4% diagnostic accuracy. The median of mean velocity (m/s) was 3.09 in the malignant group and 1.35 m/s in the benign group. In a study conducted by Sravani N., *et al*. (2020) on 175 breast masses, shear wave parameters were significantly higher in the malignant group compared to the benign group. The average mean velocity in the malignant group was 9.1 m/s compared to 2.1 in the benign group, with a sensitivity of 97.6% and specificity of 61.1% [14].

Also, there was a significant difference between the 4 ORADS groups (ORADS 2-4) in terms of mean elasticity (kPa) (χ^2 = 18.905, p = < 0.001), median range (kPa) (χ^2 = 19.724, p = < 0.001) and mean velocity (m/s) (χ^2 = 22.344, p = < 0.001), with all three parameters being highest in the USG ORADS 5 group. A few endometriomas were seen as solid masses because they are protean in their ultrasound appearance, and the rest were seen as solid cystic lesions due to the presence of blood products. Their mean elasticity (kPa) was 3.48 kPa, and mean velocity (m/s) was 1.05 m/s, which was in the benign range. A study was conducted on the diagnostic significance of multiparametric ultrasound imaging in detecting ovarian tumour-like formations by Stasiv I., *et al*. Strain elastography, along with US and Colour Doppler, was done on para-ovarian cysts, follicular cysts, corpus luteal cysts, and endometriomas. Endometriomas were found to have a slightly higher elasticity compared to the other cystic lesions [15].

In the past, very few studies have been done on the role of sonoelastography in ovarian masses using strain elastography. Strain imaging is a qualitative technique where relative stiffness differences are displayed. The primary limitation is the uncertain applied stress, which makes it impossible to determine the tissue's young modulus or elasticity in absolute terms. In contrast, the shear wave produces quantitative data by measuring the velocity produced by an acoustic radiation force or a mechanical vibration device.

A similar study was done by Herek D., *et al*. to characterise ovarian masses using US strain elastography, and results were derived in terms of elastogram patterns and strain ratios. Their results were quite contradictory to the present study, as malignant masses showed softer tissue properties than benign and cystic lesions. Two different observers performed the strain elastography and obtained an average strain ratio of 9.8 and 9.59 for cystic lesions, 8.6 and 8.6 for benign solid lesions and 2.48 and 2.2 for malignant lesions, respectively. The softer nature was attributed to necrosis in the malignant lesions of the ovary [16].

However, in the present study, malignant ovarian masses were found to have harder tissue properties and higher elasticity indices (kPa and m/sec), like the malignant masses of thyroid and breast. This difference in results might be due to a difference in technique, as they used strain elastography instead of shear wave elastography. Also, this might be attributed to different software and the placement of their second ROI on the entire lesion area, which might have incorporated the bulk of the necrotic tissue. However, in our study, the ROI for the shear wave was kept in solid, non-necrotic areas wherever possible.

But there is still a lack of research on the role of shear wave sonoelastography in differentiating benign and malignant ovarian masses. This reinforces the need for more studies that could prove the potential role of shear wave sonoelastography. Further, more studies comparing strain and shear wave elastography are also needed.

The secondary objective of the present study was to ascertain if SWE values are associated with the aggressiveness of malignant masses in terms of their histological grading. In our study, high-grade malignant tumours were found to have a higher tissue elasticity compared to low-grade tumours. This contrasted with a study by Xie M., *et al*. in which they performed strain elastography in 64 serous ovarian carcinomas comprising 39 high-grade and 25 low-grade. Their study predicted a higher tissue stiffness in low-grade lesions with

a mean elasticity score of 3.4 compared to the mean elasticity score of 2.08 in high-grade lesions. They attributed the low tissue stiffness in high-grade tumours to extensive necrosis [17]. This discordance might be because they used strain elastography with an elasticity score, a qualitative parameter. Their ROI was larger, thereby incorporating a large amount of necrotic area of the mass, which has been described as pseudo-solid by the authors. In contrast, the present study used shear wave technology and the ROI was placed in solid non-necrotic areas wherever possible.

Limitation of the Study

Our study had a few limitations. The sample size was only 56, of which only 19. Though we kept the ROI majorly in the solid areas, in very few cases, like endometriomas and serous cystadenoma, the ROI was kept in non-solid areas. Although there are a few studies using strain elastography, there is a lack of research on the role of transabdominal shear wave elastography in differentiating between benign and malignant ovarian masses. Moreover, the maximum depth of SWE is limited to 8cm; therefore, deep-seated lesions and obese patients cannot be included. Operator dependence, variability in tissue stiffness, and potential influence from cyst fluid content are other limitations. Despite all these limitations, with more extensive research, transabdominal shear wave elastography will stand out as a potential, cost-effective, radiation-free technique that can be used to differentiate benign and malignant ovarian masses, and its potential in monitoring treatment response can also be explored [18].

Future Prospects

Recently multimodal ultrasound artificial intelligence-based model, including ultrasound elastography, exhibited excellent diagnostic performance and quantified the contribution of key features, providing a reliable imaging tool for the early and precise diagnosis of ovarian malignancies [19].

Conclusion

Shear wave elastography (SWE) shows potential as a non-invasive tool to assess ovarian tissue stiffness, potentially aiding in the differentiation between benign and malignant ovarian masses by measuring the difference in tissue elasticity, with increased stiffness often indicating a higher likelihood of malignancy; however, further research is needed to establish clear diagnostic criteria and optimise its clinical application in evaluating ovarian masses.

Highlights

- Ovarian masses are a substantial diagnostic challenge to radiologists.
- Transabdominal shear wave elastography has a significant role in the characterization of complex ovarian masses.
- The clinical impact of predicting the likelihood of malignancy is crucial for optimal patient management.

Ovarian masses are a diagnostic challenge. Ultrasound Elastography has a significant role in their characterization. The clinical impact of predicting malignancy is crucial for optimal management.

Ethics Approval and Consent to Participate

A written approval was obtained from the subject.

Consent for Publication

The authors consented to the submission of the manuscript and publication. They disclosed no competing interests or relevant relationships.

Data and Materials Availability

The cases and images are available from the Department of Radiodiagnosis, Vardhman Mahavir Medical College, and Safdarjung Hospital, New Delhi, India.

Authors' Contributions

NB, the corresponding author, designed and revised the work, interpreted the data, and submitted the case. NB has approved the submitted version for publication. SN and NB* drafted the work and approved the submitted version for publication. RM has revised the manuscript and approved the submitted version for publication. RM and AB have revised the work. No disclosure. All authors read and approved the final manuscript.

Acknowledgements

We wish to thank the staff in our department for their support and cooperation throughout the study. All subjects were acknowledged for participation in this research.

Conflict of Interests

The authors declare no conflict of interest.

Funding Support

This research did not receive any financial grant from funding agencies in the public or commercial sectors.

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