ORIGINAL ARTICLE

Diagnostic Accuracy of Doppler in Identifying Malignant Ovarian Neoplasms Taking Histopathology as Gold Standard

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ABSTRACT

Objective: To determine the diagnostic accuracy of Color Doppler and Spectral Doppler in identifying malignant ovarian neoplasm using histopathology as the gold standard.

Study Design: Cross section validation

Place and Duration of Study: The study was carried out in Radiology Department in collaboration with the Pathology department at Rawalpindi Medical University and Allied Hospitals, Rawalpindi, for a period of 11 months, from May 2015 to April 2016.

Material and Methods: Patients with a clinically palpable ovarian mass or ovarian masses detected incidentally on gray scale ultrasound, who underwent surgery or biopsy within one month of Doppler examination were selected by consecutive (non-probability) sampling. A total of 153 patients were then examined by Duplex ultrasonography. Flow score, Resistive index (RI) and Pulsatility index (PI) were recorded for each patient. Post-surgical histopathology of the excised ovarian mass or tissues as benign or malignant was collected and diagnostic efficacy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Duplex USG in identifying malignant ovarian neoplasms was calculated.

Results: Diagnostic accuracy of Doppler ultrasound in identifying malignant ovarian neoplasm has been calculated as 95.4%, sensitivity 86.2%, specificity 97.58%, positive predictive value 89.28% and negative predictive value 96.8% in comparison with the gold standard of histopathology.

Conclusion: The study concludes that Doppler ultrasound is a reliable and dependable technique in the diagnosis of malignant ovarian neoplasm, however though Doppler parameters have good accuracy histopathology remains the gold standard due to limitations of the Doppler modality in pelvic inflammatory lesions.

Key Words: *Biopsy, Doppler Ultrasound, Malignant Ovarian Neoplasm, Pulsatility Index, Resistive Index.*

Introduction

Ovarian malignancy is the third most common gynecological malignancy after cervical and uterine cancer, being 7th most common malignant tumor amongst women.[1] One in every 75 women is at risk of developing ovarian malignancy and one in every 100 women with ovarian cancer dies.[2] Incidence of ovarian cancer increases with advancing age whereas multiparty and early age at first birth, are associated with lower risk. Positive personal or family history of breast or ovarian cancer also increases the risk of developing ovarian malignancy.[1,2] Preoperative classification of ovarian masses, particularly to identify malignant mass, is extremely helpful in optimal patient management with minimum morbidity.[3] Good and reliable preoperative assessment of ovarian tumors with confident identification of malignancy helps in appropriate referral of women to gynecologic oncological care and women with benign disease for conservative management or surgery.[4] Conventional gray scale 2D ultrasound or even color Doppler is sometimes unable to differentiate between benign or malignant neoplasms or inflammatory / infective masses or physiological self-limiting corpus luteal hematomas which generally do not need surgical or medical treatment unless except in rare occurrence of hematoma rupture.[4,5] Clinically these tumors may be asymptomatic, incidentally seen on routine ultrasound examination or patient may present with acute emergency like torsion or rupture of a mass.[3,4,5]

Doppler ultrasound uses sound waves to detect blood flow hence it is considered to be an effective modality to detect malignant masses as malignant neoplasm show prominent flow signals on color doppler likely due to neo angiogenesis, in contrast to benign lesions.[3,6] The color content of the tumor probably reflects tumor vascularity better than any other Doppler parameter.[3] A color score is assigned to describe the amount of blood flow within the tumor: color score 1 being no detectable blood flow; score 2 to a minimal flow; score 3 with moderate flow; and color score 4 to a highly vascular mass.[7] Benign lesions show peripheral color flow whereas malignant lesions exhibit color flow at the periphery of the mass, as well as central, intra-lesional, septal and solid intra tumoral flow.[7] The neo angiogenesis within a malignant mass are made up of abnormal vessels, without any regulated blood flow. These new formed vessels have no smooth muscles within their walls and also contain multiple arteriovenous shunts. Therefore a malignant mass shows low-impedance flow (low pulsatility index < 1.0) and (low resistance index < 0.4).[6,7] Study by Prasad et al concluded that analysis of color flow data as a predictor of malignancy had a sensitivity of 100% and negative predictive value of 100% while specificity and positive predictive value were 80% and 36% respectively.[7] In one study, 92.59 % of malignant tumors showed RI less than 0.6 in contrast to only 9.09 % of benign tumors.[8] Studies also indicate that raised serum levels of ovarian tumor markers for example CA-125 are also associated with malignancy, but recent studies suggest Doppler assessment to be superior in discriminating benign and malignant ovarian neoplasms.[2] Absence of color flow seems to be accurate for labeling a mass as benign and exclude any malignancy, but some misdiagnosis may occur in cases of metabolically active benign masses like inflammatory lesions or tubo-ovarian abscess. However, spectral Doppler along with color flow is useful in identifying malignant ovarian neoplasm. Vaginal and per abdominal gray scale and Doppler ultrasound (Duplex scan), along with serum CA-125 levels, family history and genetic history (BRCA-1, BRCA-2) may aid in early diagnosis of ovarian cancer but various research projects are still in process.

A thorough search of the literature revealed that there has not been much work done on the preoperative identification of malignant ovarian tumor with respect to Pakistani population. The simple Doppler USG parameter of resistive index is not studied much locally or internationally due to recent development of expensive and time consuming cross sectional imaging. This study was an effort to determine the diagnostic accuracy of Color Doppler and Spectral Doppler in identifying malignant ovarian neoplasm in Pakistani population using histopathology as the gold standard.
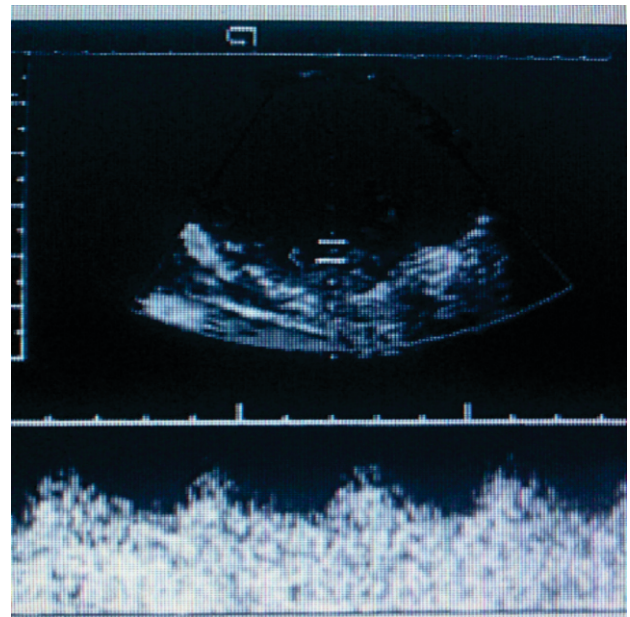
Fig 1: Cystic Mass with Papillary Projection Showing Low Resistant Spectrum Having Ri of 0.23 which came out to be Serous Cystadenocarcinoma on Histopathology
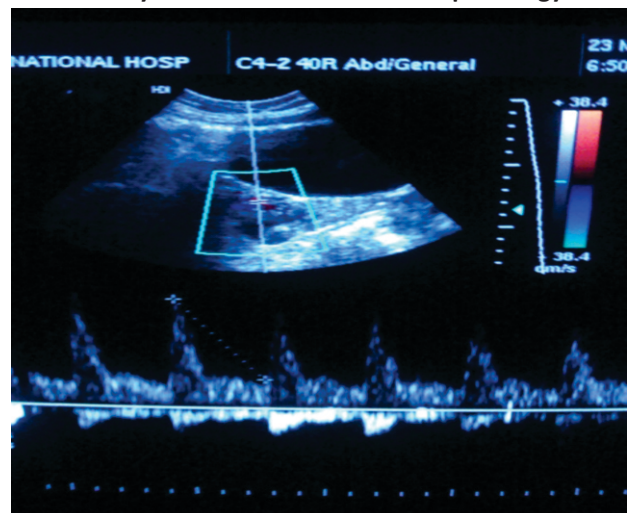
Fig 2: Solid cum Cystic Mass Showing High Resistive Spectrum and RI of 0.72. On Histopathology, It Came Out To be a Fibroma

Material and Methods

After approval by the Ethical Committee cross sectional validation study was carried out. The study was conducted in the Radiology Department in collaboration with the pathology department at Rawalpindi Medical University and Allied Hospitals, Rawalpindi. The study was carried out for 11 months, from May 2015 to April 2016. The study population comprised 153 patients with ovarian mass, selected by consecutive (non-probability) sampling; either detected incidentally on gray scale ultrasound or referred from gynecology department for USG Doppler study to Radiology Department Rawalpindi Medical University and Allied Hospitals, Rawalpindi. An informed consent was taken and then patient was subjected TOSHIBA NEMIO XG (TA 312) real time Ultrasound and Doppler scanner. 3.75 MHZ sector curvilinear transducer was used by trans-abdominal approach, and B Mode ultrasonography, Color Doppler and Spectral Doppler of patient was performed by the resident doctor and findings were confirmed by the consultant. The lesion was analyzed at high sensitivity settings with lowest pulse repetition frequency without aliasing. Three readings each of Pulsatility Index (PI) and Resistive Index (RI) values were calculated and the lowest PI and RI were recorded. Patient was then referred back to the gynecologist. Those patients who underwent surgery or biopsy within one month of Doppler examination were only included in the study. Excised ovarian mass or tissues were evaluated by team of consultant histopathologists in Pathology department, Rawalpindi Medical University and Allied Hospitals, Rawalpindi. Histopathologists had no prior information of the doppler findings. Histopathology results were directly obtained from the pathology department through patient's hospital admission number. Doppler USG results were compared to histopathological results for confirmation of malignancy. The data was collected with the help of proforma attached and diagnostic efficacy, sensitivity, specificity, positive predictive value and negative predictive value of Doppler in identifying malignant ovarian neoplasms were calculated by a 2 X 2 table. Data was entered and analyzed in SPSS version 10. Descriptive statistics were calculated for both qualitative and quantitative variables. For qualitative variables like marital status,

parity and intra tumoral color flow, frequency / percentages were calculated and for quantitative variables like age, PI and RI, mean and +/- SD were calculated.

Results

This was a cross sectional validation study conducted on 153 patients. All were female, who were referred for Duplex ultrasound to evaluate clinically detected abdominopelvic mass or incidental ovarian mass or masses, on gray scale ultrasound, (Irrespective of their age or menstrual status). The study population was in the age group 10 to 65 years. Out of the total sample of 153, married women were 111 (72.5%) and unmarried women were 42 (27.5%). 49 (32%) had 0 parity, 10 (6.5%) had 1 parity, 31 (20.3%) had 2 parity, 36 (23.5%) had 3 parity, 20 (13.1%) had 4 parity, 5 (3.3%) had 5 parity and 2 (1.3%) had 6 parity. The mean parity was 1.94 with a standard deviation of +/-1.619. Demographic characteristics of patients are briefly summarized in table I, as under;

Table I: Demographic Characteristics of Patients with Ovarian Carcinoma (N=153)

No	Characteristics	No. of patients (N)	Percentage %	Mean/Median (SD)
I	Age (Years)	153		34.5 +/- 11.802
II	Age Group (Years)			
	11 to 20	21	13.7	
	21 to 30	44	28.8	
	31 to 40	42	27.5	
	41 to 50	27	17.6	
	51 to 60	17	11.1	
	61 and above	2	1.3	
III	Marital Status			
	Married			
	Unmarried			

Calculations according to 2 x 2 table from the data collected, as shown in Table II

Table II: Diagnostic Accuracy of Doppler in Identifying Malignant Ovarian Neoplasm Taking Histopathology as Gold Standard (N=153)

Color Doppler and Spectral Doppler	Histopathology Malignant	Histopathology Benign
Malignant	True Positive a) 25	False Positive a) 3
Benign	False Negative b) 4	True Negative c) 121

- **Sensitivity** a / a + c x 100 = 25/25+4 x 100 = 86.2 %
- **Specificity** d / b + d x 100 = 121/3+121 x 100 = 97.58 %
- **Positive predictive value (PPV)** a / a + b x 100 = 25/25+3 x 100 = 89.28%
- **Negative predictive value (NPV)** d / c + d x 100 = 121/4+121 x 100 = 96.8 %
- **Diagnostic Accuracy** a + d / a + b + c + d x 100 = 25+121/25+3+4 +121 x 100 = 95.4 %

Statistical analysis of the current study revealed that overall diagnostic accuracy of Doppler ultrasound in identifying malignant ovarian neoplasm is 95.4% which is comparable with gold standard histopathological biopsy. Sensitivity was found to be 86.2% and specificity 97.58%. Positive predictive value was 89.28% and negative predictive value was calculated to be 96.8%.

Discussion

Doppler ultrasonography is noninvasive, cost effective, reliable and dependable technique with acceptable diagnostic accuracy for effective preoperative classification of malignant ovarian disease, helping the clinician to decide the management of the disease and extent of surgery in case of malignancy. A study by Khalaf et al, recently demonstrated that color flow Doppler shows neo-vascularity in 88.7% of the malignant lesions, 73.6% of them has central blood flow in contrast to only 1.9% central flow in benign lesions. They also stated that the diagnostic performance of RI < 0.6 was higher.[9] The current study used a cut-off criteria of PI < 1 and RI < 0.4, to optimize the study in terms of sensitivity and specificity, 86.2% of malignant tumors showed RI < 0.4 and PI < 1, and in contrast only 13.8% of benign tumors demonstrated RI value < 0.4 and PI value < 1. Thus for identification of malignant lesion by Doppler indices, the sensitivity of RI and PI was 86.2% and specificity of 97.58%. However another local study reported different results, Majeed H et al reported in 2011 a sensitivity of only 18.18%, specificity of 84.61% and diagnostic accuracy of 64.86%, taking a threshold of 0.4 for RI.[10] This could be explained by newer USG machines having better resolutions with per abdominal approach. [11]However investigations to compare doppler parameters of an ovarian mass by per abdominal and trans-vaginal approach are further in plan.

Doppler has no radiation exposure and side effects as compared to other modalities; histopathology still remains the gold standard due to limitations of the Doppler modality in benign inflammatory or infective lesions which may increase local blood flow and reduce resistive index mimicking neo-vascularization in malignancy as also observed in 2 false positive cases of tubo-ovarian abscess and 1 false positive case of rupture corpus luteal cyst hematoma in current study. Ultrasound detects and

identifies most of these as physiological cysts, which are not an indication for surgery. Physiological cysts include simple cysts with no internal septations or any solid component; for example follicular and corpus luteal cyst but occasionally these adnexal cysts may have low Doppler indices (low RI and PI) and this may decrease the specificity of our RI and PI measurements.

Our results are similar to other recent reports, which emphasize that although malignant lesion shows abundant vascularization with low resistance flow but some benign lesions (e.g. tubo-ovarian abscesses and chocolate cysts (endometriomas) may also show this pattern which affected the results. Khurana et al reported in 2016 that Color Doppler showed increased vascularity in 100% of malignant tumors in contrast to only 54.24% of benign tumors. [12]Vice versa, a malignant lesion could have multiple vascularized areas with variable neo angiogenesis and hence variable flow resistance.[13] In order to reduce these biases, all aspects of the lesions are to be evaluated with thorough spectral analysis of all the vascularized areas within the lesion to calculate minimum RI for detecting malignancy. Another limitation of our study was that comparisons between different radiological modalities like CT and MRI is not drawn which is in plan to explore in further studies. Mathieu et al suggested that sensitivity and spatial resolution of ultrasound is generally better than CT /PET CT but MRI has reported greater accuracy and specificity in the diagnosis of malignant adnexal masses 89% and 84%, respectively, compared to USG having 64% and 40% respectively but they didn't study doppler parameters along with gray scale 2D USG and our study revealed doppler USG has better accuracy (97.5%) and specificity (95.4%) as compared to MRI. High cost and lower availability of cross sectional imaging and MRI, is another reason for not being the first-line imaging modality for the evaluation of adnexal masses.[14]Ormsby et al concluded that concomitant use of serial CA-125 as in the ROCA model should also increase the positive predictive value of detecting malignancy compared with USG and Doppler alone. Our study revealed a PPV of 89.2% of doppler USG alone.[15] Furthermore, evaluation of Doppler USG along with serial CA-125 levels is in plan to discriminate between benign and malignant adnexal

masses. Despite these limitations, results of our study compared to the various studies were found supportive of each other, so imparting deeper insight into the diagnostic modalities of ovarian neoplasm. This would help in the future in building confidence for successful and accurate diagnosis and to monitor the patients with this disease.

Conclusion

The study concludes that Doppler ultrasound is a reliable and dependable technique in the diagnosis of malignant ovarian neoplasm, however though Doppler parameters have good accuracy histopathology remains the gold standard due to limitations of the Doppler modality in pelvic inflammatory lesions or infective lesions which may increase local blood flow and reduce resistive index mimicking malignancy.

Conflicts Of Interest Statement and Funding

The study was conducted in public sector hospital attached to medical university. There were no sponsors involved in the study. Authors state that they have no conflicts of interest to disclose.

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