



Colour Doppler Study in Differentiating Malignancy and Benign Breast Lumps

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ABSTRACT

Background: Colour Doppler sonography and Pulsed Doppler sonography have been used for last several years to evaluate breast tumours. But there are as yet no reliable investigational standards in colour Doppler sonography to classify the lesion as benign or malignant. Another reasonable goal of breast USG suggested is to identify a sub group of masses that have a very low risk of malignancy so that the option of follow-up can be offered as a viable alternative to biopsy. Accurate differentiation between benign and malignant breast nodules could result in improved care and reduction of patient discomfort, morbidity and health care cost.

Aim of this study are to determine whether Doppler and Color flow imaging is reliable in differentiating benign from malignant breast nodules and compare and correlate the ultrasound findings with biopsy results.

Materials and Methods: This is an observational study with diagnostic test evaluation. The study population consisted of 64 women over the age of 30 years, presented with a breast nodule either on clinical examination or with mammography. Doppler sonography was performed on arterial vessels within the lesion. Multiple Doppler samples was taken from all the parts of the tumour, including the margins. Only the highest systolic peak flow velocity was used for statistical analysis. Doppler frequency spectra was analysed for peak systolic velocity (V_{max}), resistance index and pulsatility index. Statistical analysis was done with SPSS v20 software. Biopsy taken from all lesions and results were compared with Doppler results.

Results: Blood flow parameters RI, PI and peak systolic velocity showed significant difference between benign and malignant. The cutoff values for these parameters were determined by plotting ROC curves. In our study RI and PI showed higher values compared to benign tumors, due to increased impedance in these lesion.

Conclusion: We arrived at cut-off value for RI and PI by drawing ROC curves. $RI > 0.61$ and $PI > 0.98$ is significant for malignancy.

Keywords: Doppler, Resistivity index (RI), Pulsatility index(PI), Peak systolic velocity (V max).

INTRODUCTION

Studies indicate that as India becomes westernized, the incidence rate for breast cancer increases¹. A 2005 study conducted by the International Association of Cancer Research,

based in Lyon, France, projected that there would be 250000 cases of breast cancer in India by 2015, a 3% increase per year. Currently, India reports roughly 100000 new cases annually.² Colour Doppler sonography and Pulsed Doppler

sonography have been used for last several years to evaluate breast tumours. But there are as yet no reliable investigational standards in colour Doppler sonography to classify the lesion as benign or malignant. . It is believed that the progress in the understanding of the predictive value of the different criteria utilized either in isolation, or in combination for categorizing breast nodules detected by multiple imaging methods, is a significant step towards reducing the number of biopsies with benign results.³ Spiculated lesions do not necessarily have perceptibly more blood flow than do benign lesions or normal tissues. The reason for this is that spiculated tumors are paucicellular. The relatively few tumor cells within spiculated lesions generate relatively small amounts of angiogenesis factors; thus, there is relatively little tumor neovascularity.

Additionally, desmoplasia requires little blood flow. On the other hand, most circumscribed malignant nodules are markedly more vascular than normal tissues or benign nodules. The much larger numbers of tumor cells generate abundant angiogenesis factors. Furthermore, the extensive inflammatory infiltrates incite a hyperemic response. The combination of extensive tumor neovascularity and inflammatory hyperemia causes these tumors to be obviously hypervascular in comparison to normal tissue and benign lesions.⁴

The malignant masses were 14 to 54% more vascular than the benign masses. Whereas benign masses were 2.2 times more vascular than the surrounding tissue, the malignant masses were 5.0 times more vascular. Although the malignant masses exhibited a strong gradient in vascularity, core > periphery > surrounding tissue, the benign masses had relatively uniform distribution of vascularity.^{5,6} Contrast-enhanced power Doppler US was superior to nonenhanced power Doppler US in the demonstration and characterization of tumor vascularity in nonpalpable breast lesions.⁷

The RI and PI values in malignant breast masses shows higher values compared to benign masses, due to increased impedance in these lesions.^{8,9}

This is in contrast to low values seen in ovarian malignancy. A number of theories might account for these findings. The relatively hard and compact tissue in breast cancer as well as irregular pattern of tumor vessels and the multiple thrombotic events in tumor could be possible explanations. Schelling M et al put RI value >0.68 and PI value >1.07 as a feature of malignancy.⁸

Peters Engl et al, evaluated the role of colour-coded and spectral Doppler sonography and a resistivity index of > or = 0.70 was considered characteristic for malignant masses. This value has got a sensitivity of 82% and a specificity of 81%.¹⁰ Thus malignant breast nodules show high PI and RI values, but no commonly agreed cut off values can be found in literature.

Power Doppler measures amplitude of blood flow rather than direction or velocity as in color Doppler. The pattern of vascularity of a breast lesion on ultrasound may help to predict the likelihood of malignancy when used with other sonographic criteria. Colour and power Doppler alone have a sensitivity and specificity of 85% and 79% respectively using resistivity index and pulsatility index as parameters. But a combination of grey - scale imaging and Doppler achieved a sensitivity and specificity of 97% and 96% respectively⁸ Thus the individual diagnostic performance of gray-scale imaging and color Doppler sonography in palpable breast disease is further enhanced using multiple logistic regression to combine independently significant parameter.

Lee S K et al concluded that color Doppler to be easier and more efficient in detecting the flow signals of neovascularity in breast tumor.⁶ But power Doppler exhibits a higher sensitivity in detecting the malignant breast tumors. Doppler features suggestive of malignant lesions were the presence of both peripheral and central vascularity (odds ratio, 6.0), presence of penetrating vessels (odds ratio, 5.4), and presence of branching vessels (odds ratio, 13.7). Power Doppler sonography was more sensitive than color Doppler sonography in detecting vascular signals.¹¹

MATERIALS AND METHODS

Study design: Observational study with diagnostic test evaluation.

Study setting: Study was conducted at Dept of Radiodiagnosis, a tertiary care centre with advanced services and one of the major referral centres in central Kerala. The study was performed for a period of one year.

Study population: The study population consisted of women over the age of 30 years who visited the mammography unit at our hospital. The patients were recruited when nodules were detected on mammography and where the nodules were palpable on clinical examination.

Inclusion criteria: Over 30 years of age, presented with a breast nodule either on clinical examination or with Mammography, biopsy had to follow for cytological and histological results

Exclusion criteria: Participants not willing to undergo histopathological evaluation by biopsy or FNAC, Subjects already underwent biopsy/FNAC, prior to USG examination, BI-RADS category 1(No lesion found), 2(includes benign lesions like breast cyst, breast implants etc) and 6(already biopsy proven malignancy)

Sample size: All patients studied during one year period were taken as samples. Once a breast nodule was noted on mammography, or on clinical examination, the researcher performed a doppler ultrasound examination on patients who agreed to participate in the study. Sample size was calculated using the Buderer's formula. $(S_n) = (z^2 \times (S_n \times (1-S_n))/W^2)/P$ $N(S_p) = (z^2 \times (S_p \times (1-S_p))/W^2)/(1-P)$

Where S_n =sensitivity, S_p =specificity, $Z=1.96$ (for 95% CI), W = precision, P = prevalence. of breast cancer in the sample to be studied was assumed to be 20% from data collected from hospital records. W was set as 0.20. The sample size thus calculated was obtained as 56. In our study we include 64 subjects.

Method: Each participant was asked to complete and sign informed consent. Included with the consent form was information concerning the study and procedures that would be performed.

Participants were interviewed to collect personal and clinical data. Participants were free to withdraw consent and to refuse participation in the study at any time. A structured, pre-prepared case proforma (CP) was used to enter the clinical history, physical examination findings, investigations-sonography and histopathology findings.

Breast Doppler ultrasound studies were performed with Siemens Acuson X300 USG machine using a high frequency (-7.5 MHZ) linear array transducer (VF 13-5 probe). Confirmation of ultrasound results was made by histopathology done by pathologist. The tissue diagnosis was obtained in all cases. Later the tissue diagnosis results were correlated with sonological findings by statistical analysis.

Color Doppler assessment: The Color Doppler box was enlarged to include the lesion and a margin of normal breast tissue and thus maximize sensitivity and minimize flash artefacts. The scanning plane was selected for optimal visualization for vascularity. Color gain was set at a level where the background color was just suppressed and a small vessel could be detected. Care was taken not to apply pressure with the probe as this has previously been found to obliterate the small, low-pressure vessels associated with breast lesions. Doppler sonography was performed on arterial vessels within the lesion. Vascularity and distribution of vessels within the lesion was noted down. Multiple Doppler samples was taken from all the parts of the tumour, including the margins. Only the highest systolic peak flow velocity was used for statistical analysis. Doppler frequency spectra was analysed for peak systolic velocity (V_{max}), resistance index and pulsatility index where

Data analysis: Cross tabulations were employed to present descriptive data. Descriptive data is therefore presented as cross tables and graphs enhanced by p-values of tests done to prove statistical significance.

OBSERVATION AND RESULT

RELATION OF VASCULARITY OF THE MASSES WITH TISSUE DIAGNOSIS

vascularity (vas) * final diagnosis(fn) Cross tabulation

		fn		Total
		Malignant	Benign	
Count		38 86.4%	6 13.6%	44 100.0%
Present	% within vas			
Vas	% within fn	88.4% 5	28.6% 15	68.8% 20
Absent	% within vas	25.0%	75.0%	100.0%
	% within &	11.6%	71.4%	31.2%
	Count	43	21	64
Total	% within vas	67.2%	32.8%	100.0%
	% within fn	100.0%	100.0%	100.0%

Vascularity	Final Diagnosis		Total
	Malignant	Benign	
Present	38	6	44
Absent	5	15	20
Total	43	21	64

On ultrasound, Doppler flow assessment detected vascularity in 44 breast masses, in which 38, (86.4%) were malignant and 6 (13.6%) were benign. The non-vascular lesions showed that 5(25%) were malignant and 15 (75%) of nodules were benign. Doppler flow assessment of the vascularity of nodules as a predictor of malignancy shows that malignant nodules more

often had an increased vascularity while benign nodules did not show increased angiogenesis. Vascularity within malignant mass lesion showed a specificity of 71.4% and sensitivity of 88.4%. The PPV, NPV and accuracy were 86.4%, 75% and 82.8%. Pearson Chi-Square test showed a p-value 0.000 which indicated that the test between the variables was statistically significant.

RELATION OF VASCULARITY OF THE MASSES WITH TISSUE DIAGNOSIS

vascularity (vas) * final diagnosis(fn) Cross tabulation

		fa		Total
		Malignant	Benign	
Count		38 86.4%	6 13.6%	44 100.0%
Present	% within vas			
vas	% within fn	88.4% 5	28.6% 15	68.8% 20
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	% within fn	100.0%	100.0%	100.0%

Vascularity	Final Diagnosis		Total
	Malignant	Benign	
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Absent	5	15	20
Total	43	21	64

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RELATION OF VESSEL DISTRIBUTION OF THE MASSES WITH TISSUE DIAGNOSIS

vessel distribution (dis) *final diagnosis(fn) cross tabulation

		fn		Total
		Malignant	Benign	
dis	Count	28	0	28
	central %within dis	100.0%	0.0%	100.0%
	% within fh	73.7%	0.0%	63.6%
	Count	10	6	16
Total	Peripheral% within dis	62.5%	37.5%	100.0%
	% within fii	26.3%	100.0%	36.4%
	Count	38	6	44
	% within dis	86.4%	13.6%	100.0%
		100.0%	100.0%	100.0%

Vessel Distribution	Final Diagnosis		Total
	Malignant	Benign	
Central Peripheral	28	0	28
	10	6	16
Total	38	6	44

According to Table 5.14 central distribution of vessels is seen exclusively in malignant lesions (28 cases). Six benign lesions which showed vascularity showed peripheral vascularity. Pattern of vessel distribution showed sensitivity of 73.7% and high specificity of 100%. The PPV, NPV and accuracy were 100%, 37.5% and 53.1%. Pearson Chi-Square test showed a p-value 0.000 which indicated that the test between the variables was statistically significant.

.450000	1.000	.833
.495000	1.000	.667
.525000	1.000	.500
.555000	1.000	.333
.570000	1.000	.167
.585000	.974	.167
.595000	.947	.167
.615000	.947	.000
.640000	.895	.000
.655000	.868	.000
.670000	.842	.000
.690000	.789	.000
.705000	.684	-.000
.715000	.579	.000
.725000	.553	.000
.735000	.474	.000
.745000	.421	.000
.755000	.316	.000
.765000	.263	.000
.775000	.237	.000
.790000	.211	.000
.805000	.053	.000
.820000	.026	.000
1.000000	.000	.000

ROC CURVE ANALYSING RI AND PI: RESISTIVITY INDEX (RI)

Coordinates of the Curve for RI Test Result Variable(s): RI

Positive if Greater Than or Equal To ^a	Sensitivity	1 – Specificity
.000000	1.000	1.000

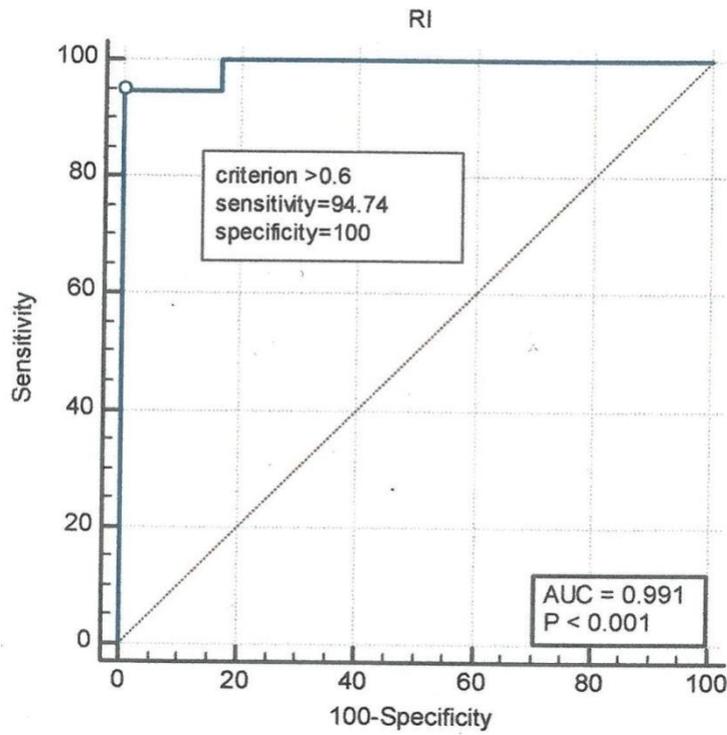
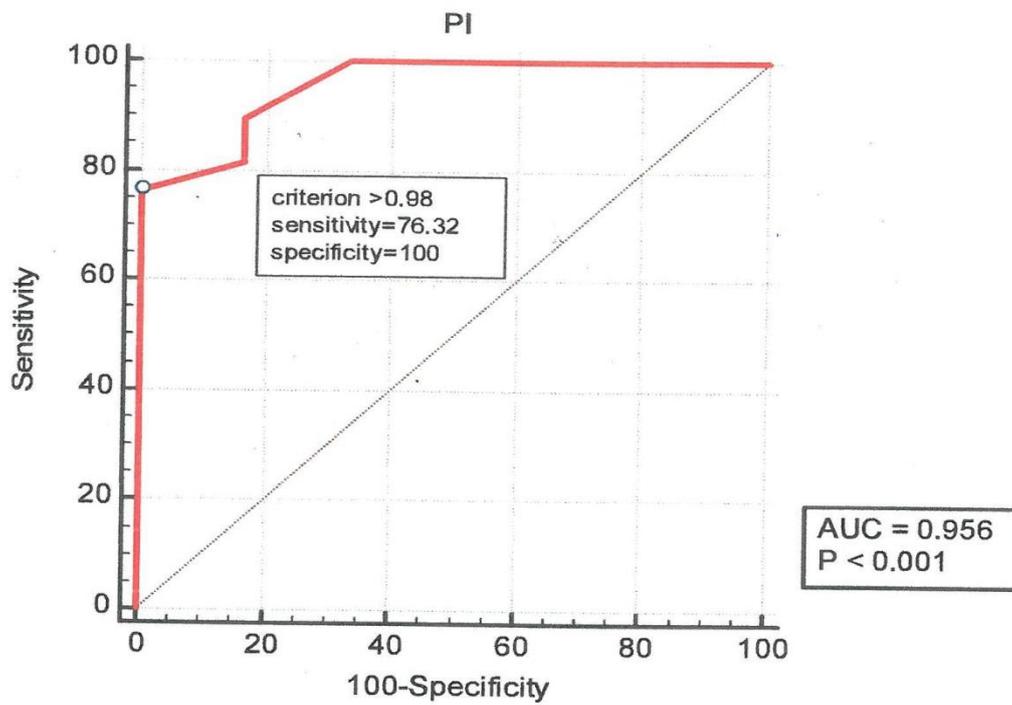


Fig ROC curve for RI (resistivity index);

PULSATILITY INDEX (PI)

Table : Coordinates of the Curve for PI Test Result Variable(s): PI

Positive if Greater Than or Equal To ^a	Sensitivity	1 - Specificity
-.300000	1.000	1.000
.750000	1.000	.833
.850000	1.000	.333
.905000	.895	.167
.920000	.868	.167
.940000	.842	.167
.965000	.816	.167
.985000	.763	.000
.995000	.711	.000
1.005000	.632	.000
1.015000	.605	.000
1.025000	.526	.000
1.040000	.474	.000
1.060000	.447	.000
1.085000	.421	.000
1.140000	.289	.000
1.190000	.263	.000
1.215000	.158	.000
1.265000	.105	.000
1.350000	.053	.000
2.400000	.000	.000



ROC Curve for PI (pulsatility index)

Variable	AUC	95% CI ^b
PI	0.956	0.848 to 0.995
RI	0.991	0.903 to 1.000

area under curve with 95% confidence interval for RI,PI

COMPARISON OF ROC CURVES

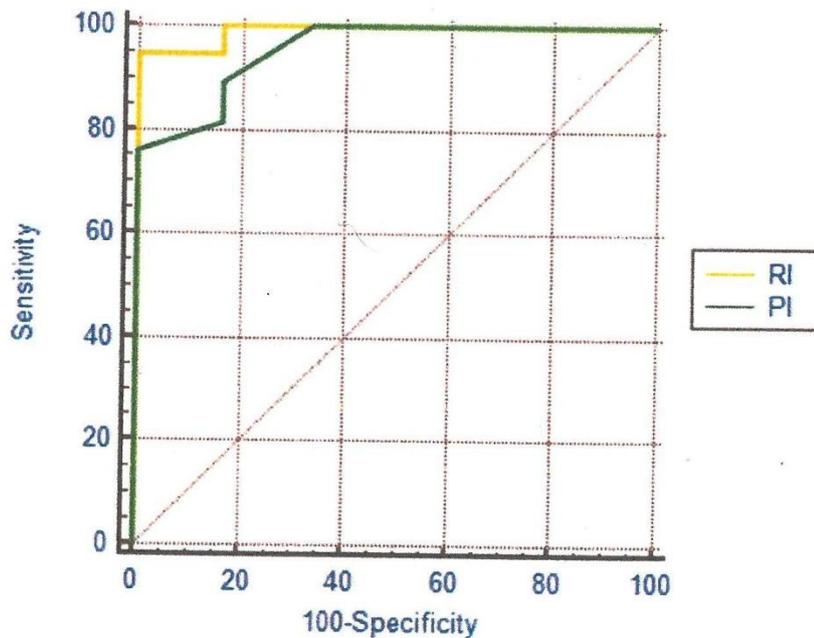


Fig: comparison of ROC curves of PI, RI

Table Doppler sonography parameters

MALIGNANCY CRITERIA	SENSITIVITY % (95% CI)	SPECIFICITY % (95%CI)
Doppler sonography n= 44		
Vascularity	88.4 (74.9- 96)	71.4 (47.8-88.6)
Central distribution of vessels	73.6 (60-86.5)	100 (54 – 100)
RI> 0.6	94.7	100
PI >0.98	76.3	100

In the present study, 88.4% masses were vascular., which correlates strongly with a study by Lee et al in which an increased vascularity was found in 94% of malignant nodules, with a 60% increase in blood flow in benign nodules⁶. In our study increased blood flow was detected in 86.4% of malignant breast nodules as opposed to in 13.6% of benign lesions. In our study 5 malignant lesions showed no vascularity most likely due to desmoplasia or paucicellular tumor⁴. Our study also observed 100% specificity and PPV for central distribution of vessels.

Blood flow parameters RI, PI and peak systolic velocity showed significant difference between benign and malignant. The cutoff values for these parameters were determined by plotting ROC curves. In our study RI and PI showed higher values compared to benign tumors, due to increased impedance in these lesions. The cutoff value for RI and PI obtained in our study were >0.61 and >0.98 . RI >0.61 showed a sensitivity of 94.7% and specificity of 100%. Similarly PI >0.98 showed a sensitivity of 76.3% and specificity of 100%. These results were comparable to data reported by most other studies^{11,12}. The results of our study were encouraging in that we were able to identify the most applicable doppler features for differentiating benign from malignant solid masses. These features have the potential to help decrease the number of biopsies performed for benign solid masses.

One limitation of our study was the results were obtained in exclusively palpable tumors with a high fraction of malignancies. Therefore study group does not reflect a normal population, where the prevalence of breast cancer is lower. Other

limitation is the single observer interpretation. So, we did not assess interobserver variability in the evaluation of these features and in the final assessments. The limitations of this study also include smaller number of patients; lack of correlation with MVD on histopathology and nonconsideration of nodal, lymphovascular and distant metastasis.

CONCLUSION

We arrived at cut-off value for RI and PI by drawing ROC curves. RI >0.61 and PI > 0.98 is significant for malignancy.

Our study shows that a combination of Doppler ultrasound should continued to be used as an adjunct to mammography and B mode sonography. The value is greatest when mammographic and B mode sonographic findings are indeterminate and the decision to biopsy or follow-up can be enhanced by the addition of Doppler ultrasound.

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