JMSCR Vol||05||Issue||02||Pages 17774-17785||February 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i2.95

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Evaluation of Doppler Spectral Indices As 'Tests' with High Sensitivity for the Provisional Diagnosis of Malignancy in Solid Breast Masses and the Recruitment of Cases for Confirmatory Tests

Authors
John N. J., Beenamol S., Ravikanth Balaji
Medical College Trivandrum Kerala

Abstract

Introduction: *The 'cut off' values of pulsatility index (PI) and resistive index (RI) described in the early literature on Doppler sonography of solid breast masses, for provisionally diagnosing malignancy had high specificity and relatively low sensitivity, the features of a 'confirmatory test'. But the current role of ultrasonography and Doppler studies of solid breast masses is to recruit cases for confirmatory tests with high sensitivity for malignancy.*

Aim of the work: *To identify 'cut off' values of Doppler spectral indices that can be used as 'tests' to diagnose breast malignancy provisionally with high sensitivity, and thus can recruit cases for confirmatory tests.*

Patients and Methods: *The values of PI and RIof flow in arterioles within 49 solid breast lesions showing vascularity were compared with the final diagnosis. From receiver operating characteristic (ROC) curves the best cut off value with a very high sensitivity was identified for each Doppler spectral index.*

Results: *The value of PI equal to or greater than 1.1, as a test, has a sensitivity of 86.1%, specificity of 92.3%, and likelihood ratio (LR+) of 11.18, for a 'provisional diagnosis' of malignancy in solid breast mass. The value of RI equal to or greater than 0.66, as a test, has a sensitivity of 88.9%, specificity of 92.3%, and likelihood ratio (LR+) of 11.545.*

Conclusions: *Presence of arterioles with either PI≥1.1 or RI≥0.66 in a solid breast mass is indicative of malignancy with high sensitivity and can be used to recruit cases for confirmatory tests like FNAC and biopsy.*

Keywords: *Solid breast masses, Doppler ultrasound, Doppler spectral indices, pulsatility index, resistive index.*

Introduction

Quite a few articles have appeared in the literature, evaluating the efficiency of morphological patterns of vascularity, semi quantitative assessment of vascularity and various spectral indices on colour Doppler ultrasound, to differentiate malignant breast masses from the benignones.

The demonstrability of new abnormal vessels of tumour angiogenesis is associated with a high risk of malignancy.[1] Early studies favoured an impresssion of malignancy in masses with demonstrable vascularity.[2]However advances in technology and equipment have led to detection of Doppler flow in many solid benign lesions.[3-11]

Morphology of the vessels with preference to their location at periphery, extension into the

centre and their branching pattern has been evaluated as a predictor of malignancy.[5]

Doppler spectral indices, namely pulsatility index (PI) and resistive index (RI) have been used to differentiate malignant breast masses from benign ones. The cut-off points of 1.4 and 0.8 for PI and RI, respectively, have been put forward for this purpose by del Cura et al; these investigators have obtained at least 80% specificity and relatively high sensitivity and positive predictive value for an impression of malignancy in breast masses showing PI or RI values equal to or greater than the 'cut off' values mentioned above.[12] However, the current role of gray scale and colour Doppler ultrasound is to identify lesions requiring FNAC/biopsy i.e., that of a 'screening test' which should have high sensitivity, even at the cost of specificity. The present study is an attempt to evaluate the efficiency of various Doppler parameters including morphological parameters of vascularity and the conventional Doppler spectral indices in differentiating the malignant lesions from the benign ones among the palpable solid masses of breast and to identify a set of cut-off values of the spectral indices giving high sensitivity for malignancy and thus can recruit cases for FNAC/biopsy.

Aims

1. To assess the efficiency of patterns of vascularity as observed on colour Doppler sonography of solid breast tumours, to differentiate malignant masses from benign ones.
2. To assess the efficiency of 'cut off' values of conventional Doppler spectral indices described in literature to differentiate benign and malignant breast masses.
3. To determine the cut - off values of the spectral indices as test criteria with high sensitivity for selecting patients for a confirmatory test like FNAC/biopsy.
4. To determine the cut - off values of the spectral indices as test criteria with high specificity which would raise strong suspicion of malignancy.

Materials and Methods

The study was carried out on patients with clinically palpable breast lumps. The study was performed between January 2008 and December 2009. All the cases, in which pathologic/definitive cytopathologic diagnosis was not obtained, were eliminated from the study. Those masses, which were found to be cystic on ultrasonography also were eliminated.

All patients were reassessed and their history, clinical details and data regarding other imaging studies including x-ray mammogram were noted. Ultrasonography including the Doppler study was performed using Aloka SSD 2000 colour Doppler scanner equipped with a 7.5 MHz linear transducer and Esaote Megas GPX colour Doppler scanner equipped with a 10 MHz linear transducer, Initially gray scale ultrasound was done and the findings and impression are noted. Colour Doppler ultrasound examination was performed in detail in each case. The presence of vascularity and the morphology of vessels with particular reference to orderliness of direction and regularity of branching were noted. Doppler spectrum was obtained from multiple points and details of the spectrum like peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI), resistive index (RI), peak systolic by end diastolic velocity ratio (S/D ratio) etc were noted.

Statistical calculations were done excluding the masses, which did not demonstrate vascularity on Doppler study. Efficiency of each Doppler parameter was calculated with the 'cut off value' described in the literature, as a 'test' to differentiate malignant tumours from benign ones. Receiver operating characteristic curve (ROC curve) was plotted for each spectral index to identify a 'cut off' value that can be used as a 'test' with high sensitivity and another 'cut off' value that can be used as a 'test' with high specificity.

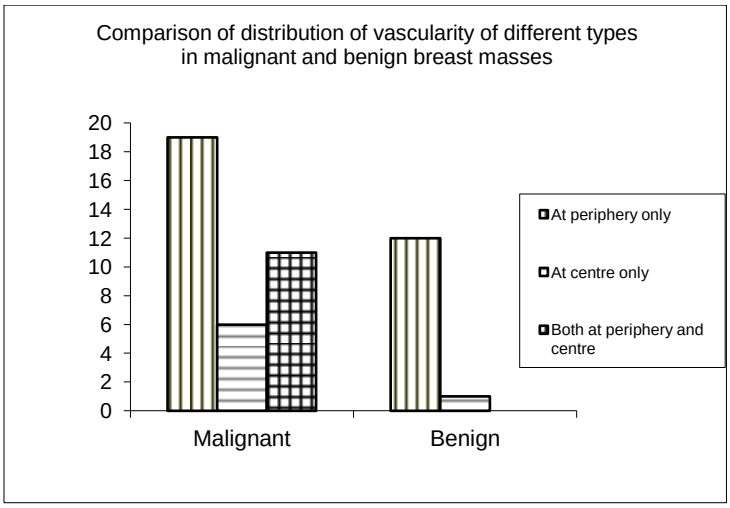
Results

The total number of cases examined was 150 out of which only 49 showed vascularity.

Amongthe 13 benign breast masses which showed vascularity on colour Doppler examination, vascularity of various types was distributed as follows; 12 cases showed vascularity at the periphery and 1 case had a small central vessel. These benign lesions distinctly lacked irregularly branching and chaotic vessels. The one benign mass, which showed central vascularity, was a fibroadenoma; no other benign histopathologic entity showed vascularity at the centre in the study group.

Among the 36 malignant breast masses which showed vascularity on colour Doppler examination, 19 had vessels at the margins of the lesion alone, 6 at the centre alone, and 11 both at periphery and centre; 6 of the last subgroup showed irregular branching pattern of the vessels. All the cases, which showed irregularly branching penetrating vessels, were malignant.

Figure 1



The mean, standard deviation (SD), maximum value, minimum value and range of observed Doppler spectral indices, namely Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV), Pulsatility Index (PI), Resistive Index (RI), of malignant and benign masses are tabulated below.

Table No: 1 Values of Doppler spectral indices in malignant and benign breast masses and statistical measures of their dispersion

	Mean	S.D.	Maximum	Minimum	Range
PSV of malignant masses (cm/s)	18.16	12.863	71	5	66
PSV of benign masses (cm/s)	7.18	3.861	17	4	13
EDV of malignant masses (cm/s)	4.247	4.348	26	0	26
EDV of benign masses (cm/s)	2.731	1.109	5.4	1.5	3.9
PI of malignant masses	1.6	0.677	4.04	0.77	3.27
PI of benign masses	0.935	0.109	1.24	0.82	0.42
RI of malignant masses	0.763	0.1	1.0	0.59	0.41
RI of benign masses	0.602	0.041	0.69	0.54	0.15

In the tables given below, the statistical calculations for efficiency of individual tests are displayed. The test criterion is given in the first cell on the left hand side of the table. When a Doppler spectral index is used as the test, it is mentioned in short form, followed by the cut-off value. "Test: PI ≥ 0.9" means that the test is detection of a PI value equal to or greater than 0.9; "test +ve" indicates the number of cases which show a PI value equal to or greater than 0.9; "test -ve" indicates the number of cases which show a PI value less than 0.9; "disease positive" means the number of cases which are positive for malignancy on histopathology/ cytopathology; "disease negative" means the number of cases which are positive for malignancy on histopathology/cytopathology.

Table No: 2 Statistical indices of accuracy of the 'test' using values of PI ≥ 1.4 for provisionally 'diagnosing' malignancy

Test: PI ≥ 1.4					
	Disease +ve	**Disease -ve**	**Total**		Sensitivity 47.22%
Test +ve	17	0	17		Specificity 100%
Test -ve	19	13	32		Positive Predictive Value 100%
Total	**36**	**13**	**49**		Negative Predictive Value 40.62%
					Likelihood ratio (LR+) Infinity

Disease +ve- Positive for malignancy

Fig: 2 ROC curve for various values of PI used as 'cut-off' value for provisionally 'diagnosing' malignancy

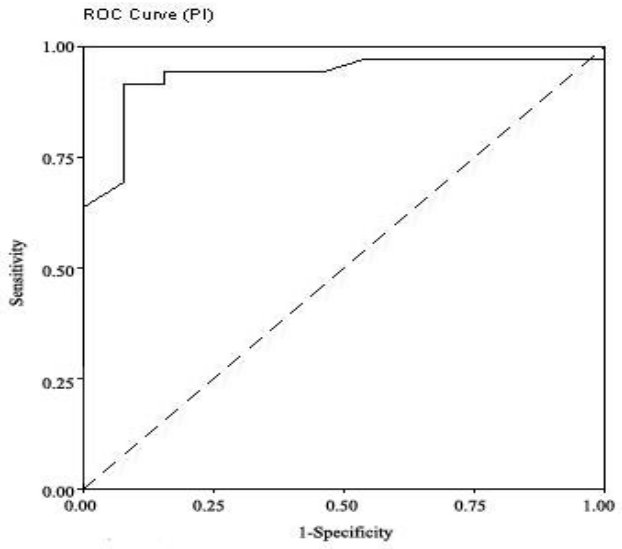


Table No: 3 Chart of Sensitivity, Specificity & Likelihood ratio for various cut-off values of PI

cut-off value of PI	Sensitivity	1 - Specificity	Specificity	Likelihood ratio(LR+)
0.795	0.972	1	0	0.972
0.83	0.972	0.923	0.077	1.053088
0.845	0.972	0.846	0.154	1.148936
0.86	0.972	0.769	0.231	1.263979
0.875	0.972	0.615	0.385	1.580488
0.905	0.972	0.538	0.462	1.806691
0.935	0.944	0.462	0.538	2.04329
0.95	0.944	0.385	0.615	2.451948
0.97	0.944	0.231	0.769	4.08658
0.985	0.944	0.154	0.846	6.12987
1	0.917	0.154	0.846	5.954545
1.015	0.917	0.077	0.923	11.90909
1.045	**0.889**	**0.077**	**0.923**	**11.54545**
1.09	**0.861**	**0.077**	**0.923**	**11.18182**
1.12	0.833	0.077	0.923	10.81818
1.14	0.806	0.077	0.923	10.46753
1.155	0.778	0.077	0.923	10.1039
1.165	0.75	0.077	0.923	9.74026
1.19	0.722	0.077	0.923	9.376623
1.225	0.694	0.077	0.923	9.012987
1.26	0.639	0	1	

1.295	0.611	0	1	
1.315	0.583	0	1	
1.335	0.556	0	1	
1.36	0.5	0	1	
1.385	0.472	0	1	
1.41	0.444	0	1	
1.475	0.417	0	1	
1.55	0.389	0	1	
1.585	0.361	0	1	
1.65	0.333	0	1	
1.76	0.278	0	1	
1.835	0.222	0	1	
1.9	0.194	0	1	
2	0.167	0	1	
2.255	0.139	0	1	
2.53	0.111	0	1	
2.74	0.083	0	1	
2.965	0.056	0	1	
3.545	0.028	0	1	

The test is positive if PI is greater than or equal to the value given in first column. Sensitivity and Specificity are given in absolute value and not as percentage; e.g.0.972 is equal to 97.2%. **The best cut-off value of PI as a test criterion with high sensitivity is between 1.046 and 1.09. It can be rounded off to 1.1 for practical purposes**

The best cut-off value of PI as a test criterion with a high level of sensitivity is between 1.046 and 1.09. It can be rounded off to 1.1 for practical purposes. This cut-off value has a sensitivity of 86.1%, a specificity of 92.3%, a positive pred-icttive value of 96.9%, a negative predictive value of 70.6% and a likelihood ratio of 11.18 in this study.

Table No: 4 Statistical indices of efficiency of the 'test' using values of PI ≥ 1.1 for provisionally 'diagnosing' malignancy

Test: PI ≥ 1.1				
	Disease +ve	**Disease –ve**	**Total**	Sensitivity 86.1%
Test +ve	31	1	32	Specificity 92.3%
Test –ve	5	12	17	Posit. Predictive Value 96.9%
Total	**36**	**13**	**49**	Neg. Predictive Value 70.6%
				Likelihood Ratio (LR+) 11.18

Disease +ve- Positive for malignancy

A 'cut off' value of PI giving very high specificity for a diagnostic impression of malignancy was looked for. A value of 1.26 affords very high specificity and it can be rounded off to 1.3 for the sake of simplicity.

Table No: 5 Statistical indices of efficiency of the 'test' using values of PI ≥ 1.3 forprovisionally 'diagnosing' malignancy

Test: PI ≥ 1.3				
	Disease +ve	**Disease–ve**	**Total**	Sensitivity 61.1%
Test +ve	22	0	22	Specificity 100%
Test –ve	14	13	27	Posit. Predictive Value 100%
Total	**36**	**13**	**49**	Neg. Predictive Value 48.1%
				Likelihood Ratio (LR+) Infinity

Disease +ve- Positive for malignancy

There was one lesion with PI value greater than 4 in the study group and it was malignant.

There were 3 lesions with RI equal to or greater than 1 in the whole of the study group; all of them were malignant. The detection of RI equal to or greater than 1, as a sign of malignancy had a sensitivity of 6% only. However it had specificity of 100% and positive predictive value of 100%.

Table No: 6 Statistical indices of efficiency of the 'test' using values of RI ≥ 0.8 for provisionally 'diagnosing' malignancy

Test: RI ≥ 0.8					
	Disease +ve	**Disease –ve**	**Total**		Sensitivity 38.8%
Test +ve	14	0	14		Specificity 100%
Test –ve	22	13	35		Posit. Predictive Value 100%
Total	**36**	**13**	**49**		Neg. Predictive Value 37.74%
					Likelihood Ratio (LR+) Infinity

Disease +ve- Positive for malignancy

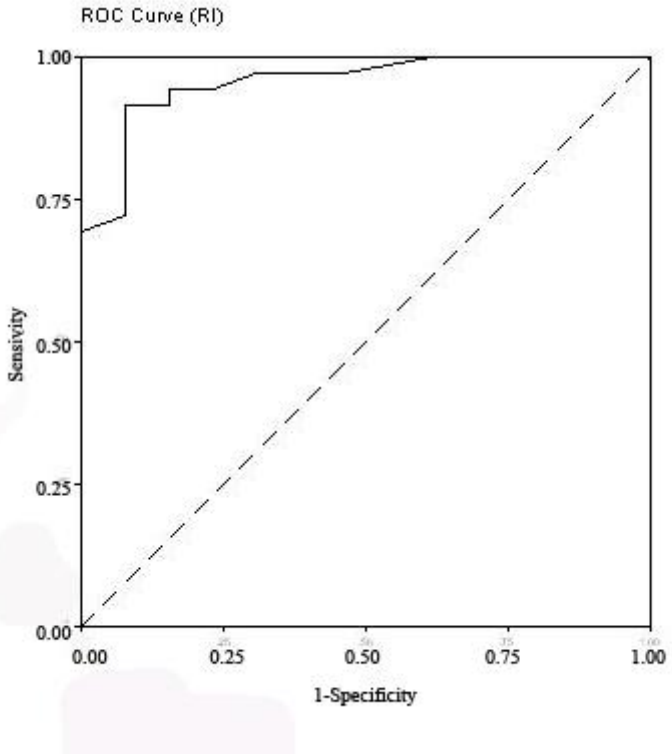


Fig: 3 ROC curve for various values of RI used as 'cut-off' value for provisionally 'diagnosing' malignancy

Table No: 7 Chart of Sensitivity, Specificity & Likelihood ratiofor various values of RI used as 'cut-off' value for provisionally 'diagnosing' malignancy

cut-off value of RI	**Sensitivity**	**1 - Specificity**	**Specificity**	**Likelihood ratio(LR+)**
0.555	1	0.923	0.077	1.083424
0.575	1	0.692	0.308	1.445087
0.585	1	0.615	0.385	1.626016
0.595	0.972	0.462	0.538	2.103896
0.605	0.972	0.385	0.615	2.524675
0.62	0.972	0.308	0.692	3.155844
0.6345	0.944	0.231	0.769	4.08658
0.6395	0.944	0.154	0.846	6.12987
0.645	0.917	0.154	0.846	5.954545
0.655	**0.917**	**0.077**	**0.923**	**11.90909**

0.665	**0.889**	**0.077**	**0.923**	**11.54545**
0.675	0.833	0.077	0.923	10.81818
0.685	0.722	0.077	0.923	9.376623
0.7	0.694	0	1	
0.715	0.639	0	1	
0.725	0.611	0	1	
0.735	0.583	0	1	
0.755	0.472	0	1	
0.775	0.417	0	1	
0.79	0.389	0	1	
0.805	0.306	0	1	
0.815	0.278	0	1	
0.83	0.167	0	1	
0.85	0.139	0	1	
0.865	0.111	0	1	
0.935	0.083	0	1	

The test is positive if RI is greater than or equal to the value given in first column.Sensitivity and Specificity are given in absolute value and not as percentage. 0.972 is equal to 97.2%.**The best cut-off value of RI as a test criterion with high sensitivity is between 0.655 and 0.665, i.e. 0.66**

The best cut-off value of RI as a screening test criterion is between 0.655 and 0.665, i.e. 0.66. This cut-off value has a sensitivity of 90.3%, a specificity of 92.3%, a positive predictive value of 96.97%, a negative predictive value of 75% and a likelihood ratio of 11.545 in this study.

Table No: 8 Statistical indices of efficiency of the test using values of RI≥ 0.66 for provisionally 'diagnosing' malignancy

Test: RI ≥ 0.66					
	Disease +ve	**Disease –ve**	**Total**		Sensitivity 88.9%
Test +ve	32	1	33		Specificity 92.3%
Test –ve	4	12	16		Posit. Predictive Value 96.97%
Total	**36**	**13**	**49**		Neg. Predictive Value 75%
					Likelihood Ratio (LR+) 11.545

Disease +ve- Positive for malignancy

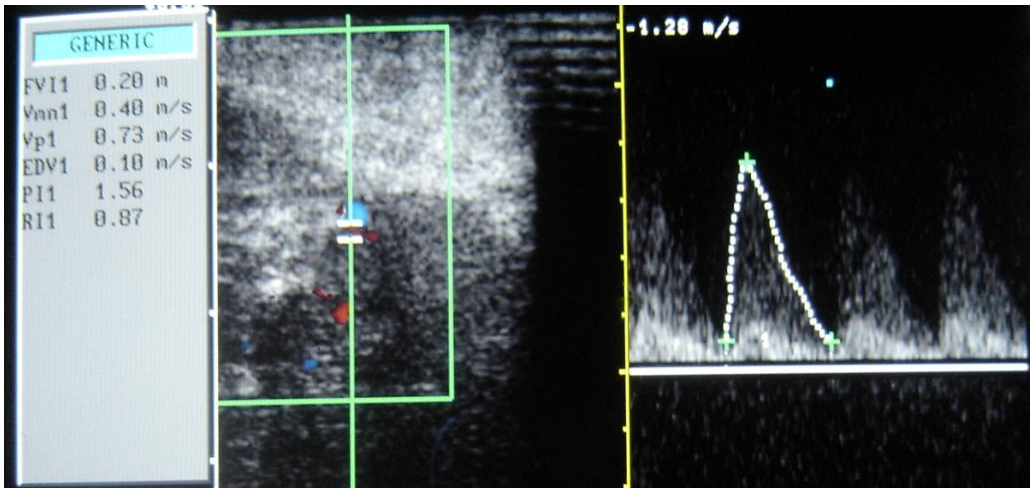


Fig. 4. Infiltrating duct carcinoma in a 78 year old patient. The lesion shows central flow. The Doppler spectral waveform has the following indices – PI: 1.56; RI: 0.87; PSV: 71 cm/s; EDV: 9cm/s. This malignant mass has high PI and RI.

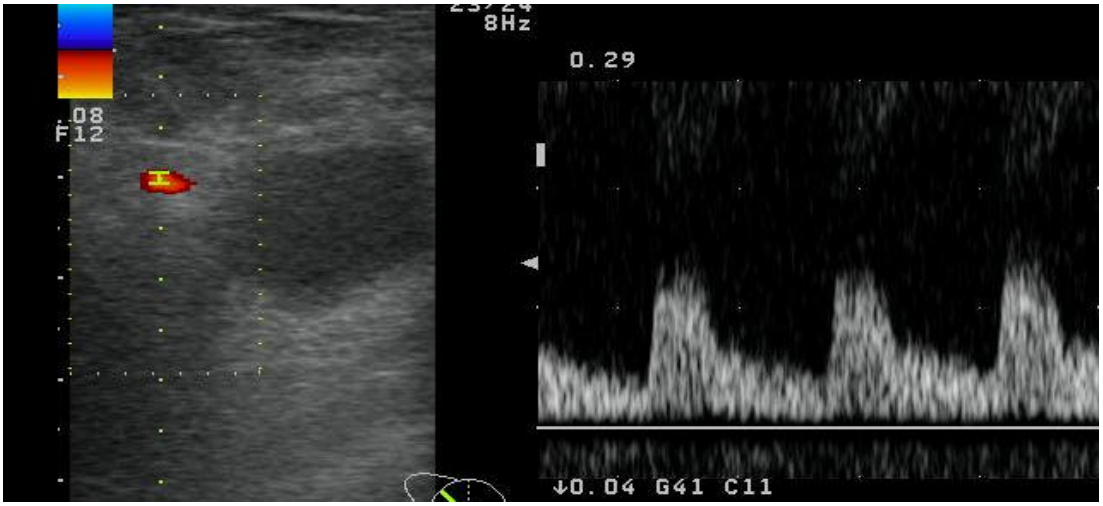


Fig. 5. Infiltrating duct carcinoma in a 52 year old patient. The Doppler spectral waveform has the following indices –PI: 0.77; RI: 0.63; PSV: 18.4 cm/s; EDV: 6.7cm/s. This malignant mass has low PI and RI.

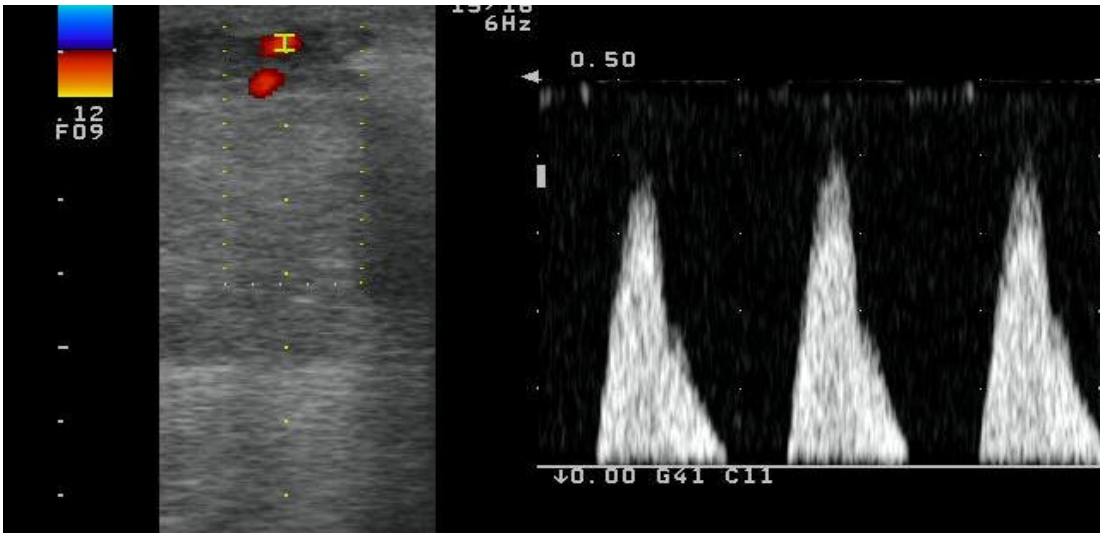


Fig. 6. Infiltrating duct carcinoma in a 49 year old patient. The Doppler spectral waveform has the following indices – PI: 4.04; RI: 1; PSV: 47.5 cm/s; EDV: 0 cm/s. This malignant mass has very high PI (greater than 4) and very high RI (equal to or greater than 1).

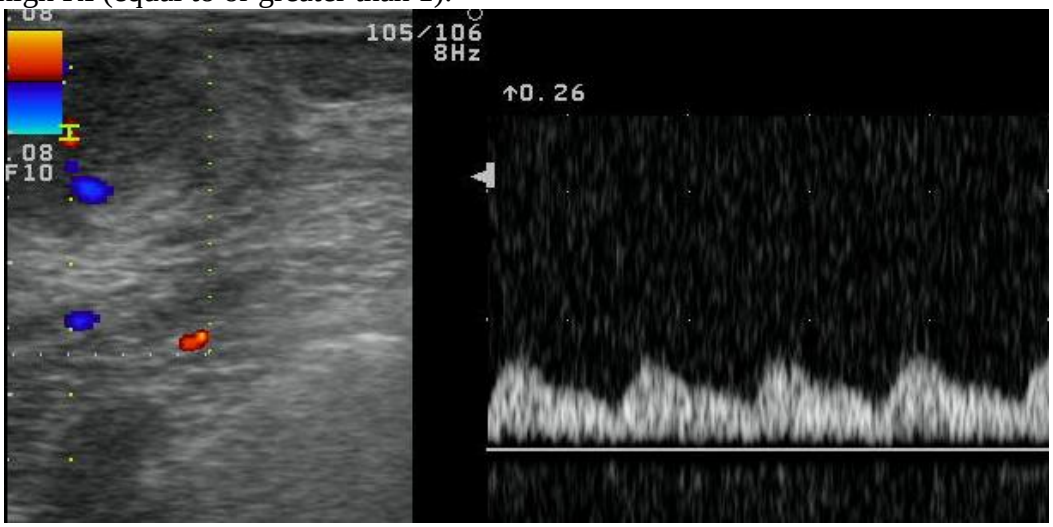


Fig. 7. Fibroadenoma with vascularity in 30 yr old patient.The Doppler spectral waveform of the vessels in the mass has the following indices –PI: 0.96; RI: 0.639; PSV: 7 cm/s; EDV: 2.5 cm/s. This benign mass has low PI and low RI.

Discussion

It has been observed that presence of vascularity detectable by colour Doppler sonographyis more common in malignant breast masses than in benign tumours. However advances in technology are making it increasingly possible to detect vessels within benign masses. For this reason, an attempt to use detection of vascularity by Doppler sonography as a 'test' to 'diagnose' malignancy provisionally is not made in this study.

The descriptive sign of irregularly branching vessels with chaotic flow appears to be useful in the diagnosis of malignant breast tumours, as all such cases were proved to be malignant. This observation is similar to that of Raza et al.[5]

Other parameters of blood flow like average number of vessels per square centimeter and average density of colour pixels, used by early workers[3,13] were not utilized in the present study, as they are semiquantitative in nature.

The average peak systolic velocity in the malignant tumours is more than that in benign ones, in the present study; however the distribution of the velocities is over a very wide range within benign or malignant tumours, resulting in wide degree of overlap on comparison of the two; this precludes the possibility of using PSV in differentiating malignanttumours from the benigno9 ones. According to many reports[14,15-18] there is no significant difference in PSV between ben-ign and malignant tumors. PSV is an angle-dependent parameter and accurate angle correction is difficult because the orientation of intratumoral vessels is often irregular.

There is no appreciable difference in the ranges of end diastolic velocity (EDV) between the benign and malignant lesions in the present study.

There is overlap between the values of PI in benign and malignant tumour groups in the present study. The efficacy of PI in diagnosing malignancy is assessed with different cut-off values in the present study; when a value of PI equal to or greater than 1.4, as suggested by del Cura[12] (31) is used to differentiate malignant tumours from benign ones, the following statistical figures are obtained – sensitivity (47.2%), specificity (100%), positive predictive value (100%) and negative predictive value (40.6%); when a value of PI equal to or greater than 1.1 as suggested by Mesaki et al[19] is used for the same purpose, sensitivity is (86.1%), specificity (92.3%), positive predictive value (96.9%), negative predictive value (70.6%) and likelihood ratio of 11.18

The relationship between sensitivity and specificity for classifying tumours as benign and malignant at various values of Doppler spectral parameter values is evaluated by analysis of Receiver Operating Characteristic curve.

Analysis of the ROC curve reveals that the best cut-off value of PI as a 'test'with high sensitivity is between 1.046 and 1.09 and this finding is close to the suggested cut-off value of 1.1 for PI in the article by Mesaki et al.[19]. The average of these values, 1.068 can be rounded off to 1.1. This cut-off value of 1.1 has a sensitivity of 86.1%, a specificity of 92.3%, a positive predictive value of 96.9%, a negative predictive value of 70.6% and a likelihood ratio of 11.18. This 'cut off' value can be used as a criterion to recruit cases for 'very specific tests', namely FNAC and biopsy.

It can be seen that the best 'cut off' value of PI as a test with high specificity is around 1.3 (Please see table no: 5). Any mass with PI equal to or greater than 1.3 should be viewed with a strong suspicion.

A PI equal to 4 or greater has been reported to be highly specific and has a high positive predictive value for diagnosing malignancy. The one case in the present study with PI greater than 4 was found to be malignant.

There is overlap between the value ranges of RI in benign and malignant groups, in the

present study, similar to that of delCura et al.[12] The efficacy of RI in diagnosing malignancy is assessed in the present study; when a value of RI equal to or greater than 0.8, as suggested by del Cura et al[12] is used to differentiate malignant tumours from benign ones, the following statistical figures are obtained – sensitivity (38.9%), specificity (100%), positive predictive value (100%) and negative predictive value (37.1.6%); the article by del Cura et al had not mentioned using ROC analysis and likelihood ratio. It is obvious that the sensitivity is unacceptably low and this cut-off value cannot be used in Doppler studies, which are used as as screening tools. However, this 'cut off' value is useful as a 'very specific test', which on being positive, should raise a strong suspicion of malignancy

Analysis of the ROC curve of RI reveals that the best cut-off value of RI as a test criterion is between 0.655 and 0.665 i.e. 0.66. This cut-off value has a sensitivity of 88.9%, a specificity of 92.3%, a positive predictive value of 96.97%, a negative predictive value of 75% and a likelihood ratio of 11.545. All these parameters are excellent for a 'screening test'with high sensitivity and this study proposes a cut-off value of 0.66 for RI for the purpose of selecting cases that need biopsy (the gold standard). The article by delCura et al[12]suggesting a cut-off RI value of 0.8 has not mentioned about having carried out ROC analysis.

An RI, equal to or greater than one, had poor sensitivity (8.3%) and negative predictive value (28.3%) but very high specificity (100%) and positive predictive value (100%). An RI, equal to one or greater, has been reported to be highly specific and has a high positive predictive value for diagnosing malignancy. In the present study there were three cases with RI equal to one and all three were found to be malignant.

The present study has a few limitations. There is technical difficulty to demonstrate arteriolar flow in many of benign breast masses and small malignant masses. Thus result of the study can be applied only on lesions demonstrating vascularity. The statistical calculations are done excludeing the masses not demonstrating vascularity. If they are included, the values of parameters of efficiency of each Doppler index are much lower. But as and when more sophisti-cated Doppler machines will be available, this draw back can be overcome partly or fully. The study sample may not be a true representative of the patient population due to 'sampling errors'

There might have been selection bias in the enrolment of cases into the study; the whole spectrum of cases may not have been studied. Ideally such a study should be taken up as a part of a population-based breast cancer screening programme which undert-akes clinical assessment, x-ray mammog-raphy and gray scale & Doppler ultrasound; this alone can avoid sampling errors and selection bias and can allow quantification of the positive impact of Doppler study on the rate of detection of breast malignancy.

Conclusions

Breast tumours with prominent vessels entering at a peripheral point and extending inward with an irregular branching pattern or chaotic flow are very likely to be malignant and should invariably undergo biopsy.

Among conventional Doppler spectral parameters, PI is the most useful in differentiating malignancy from benignity among the breast tumours with demonstrable vascularity, though sensitivity near cent per cent is not achievable. A PI value equal to or greater than 1.1 is acceptable for coming to a 'provisional diagnosis' of malignancy with high sensitivity and to select cases for FNAC/biopsy.

This study proposes an RI value equal to or greater than 0.66 to be used instead of 0.8 described in the literature, for coming to a 'provisional diagnosis' of malignancy, in view of the result of ROC analysis of RI values. This 'cut

off' value affords high sensitivity and can select cases for FNAC/biopsy.

It is reasonable to conclude that, if any lesion, considered to be 'benign' and not requiring biopsy on evaluation of clinical data, x-ray mammography and gray scale ultrasonography, shows a positive Doppler parameter mentioned above, it should undergo a definitive diagnostic procedure like FNAC, core biopsy or excision biopsy.

Breast masses having PI equal to or greater than 1.3 OR having RI equal to or greater than 0.8 should be viewed with high index of suspicion of malignancy.

Acknowledgements

The authors thank Dr. G. Vijayakumar, Professor and Head, Dept of Radiodiagnosis, Sree Mookambika Institute of Medical Sciences, Padanilam, Kanyakumari District, Kulasekharam, 629161, India for support in the conduct of the study. They acknowledge the assistance in statistical analysis provided by Dr. Harikumaran Nair G.S., Professor and Head, Dept of Radiodiagnosis, TD Medical College, Alappuzha, Kerala, India and Dr. BijuSoman, Additional Professor, AMCHSS, Sree Chitra Thirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India.

Conflict of interest: None

References

1. Folkman J. How is blood vessel growth regulated in normal and neoplastic tissue? GHA Clowes Memorial Award lecture. Cancer Res 1986;46:467-73.
2. Schoenberger SG, Sutherland CM, Robinson AE. Breast neoplasms: duplexsonographic imaging as an adjunct in diagnosis. Radiology 1988;168:665-8.
3. Cosgrove DO, Kedar RP, Bamber JC, al-Murrani B, Davey JB, Fisher C et al. Breast diseases: color Doppler US in differential diagnosis. Radiology 1993;189:99-104.
4. Rizzatto G, Chersevani R, Abbona, M, Lombardo VL, Macorig D. High resolution sonography of breast carcinoma. Eur J Radiol 1997;24:11-9.
5. Raza S, Baum JK. Solid breast lesions: evaluation with power Doppler US. Radiology 1997;203:164-8.
6. Kook S, Park H, Lee Y et al. Evaluation of solid breast lesions with power Doppler sonography. J Clin Ultrasound 1999;27: 231-237.
7. Lee WJ, Chu JS, Huang CS, Chang MF, Chang KJ, Chen KM, et al. Breast cancer vascularity: color Doppler sonography and histopathology study. Breast cancer Res Treat 1996;37:291-8.
8. Lee WJ, Chu JS, Chang KJ, Chen KM. Occult breast carcinoma: use of color Doppler in localization. Breast Cancer Res Treat 1996; 37:299-302.
9. Britton PD, Coulden RA. The use of duplex Doppler ultrasound in the diagnosis of breast cancer. ClinRaidiol 1990;42:399-401.
10. Lee SK, Lee T, Lee KR, Su YG, Liu TJ. Evaluation of breast tumors with color Doppler imaging: a comparison with image- directed Doppler ultrasound. J Clin Ultrasound 1995;23:367-73.
11. Peters-Engl CH, Fran W, Leodolter S, Medl M. Tumor flow in malignant breast tumors measured by Doppler ultrasound: an independent predictor of survival. Breast Cancer Res Treat 1999;54:65-71.
12. del Cura JL, Elizagaray E, Zabala R, Legorburu A, Grande D. The use of unenhanced Doppler sonography in the evaluation of solid breast lesions. AJR Am J Roentgenol. 2005;184:1788-94.
13. McNicholas MMJ, Mercer PM, Miller JC, McDermott EW, O'Higgins NJ, MacErlean DP et al. Color Doppler sonography in the evaluation of palpable breast masses. AJR Am J Roentgenol 1993;161:765-71.

14. Madjar H, Sauerbrei W, Prompeler HJ, Wolfarth R, Gufler H. Color Doppler and duplex flow analysis for classification of breast lesions. GynecolOncol 1997;64: 392-403.
15. Buadu LD, Murakami J, Murayama S, Hashiguchi N, Toyoshima S, Sakai S, Yabuuchi H, Masuda K, Kuroki S, Ohno S: Colour Doppler sonography of breast masses: a multiparameter analysis. ClinRadiol 1997;52:917-923.
16. Hollerweger A, Rettenbacher T, Macheiner P, Gritzmann N. New signs of breast cancer: high resistance flow and variations in resistive indices evaluation by color Doppler sonography. Ultrasound Med Biol 1997;23:851-856.
17. Choi HY, Kim HY, Baek SY, Kang BC, Lee SW: Significance of resistive index in color Doppler ultrasonogram: different-iation between benign and malignant breast masses. Clin Imaging 1999;23:284-288.
18. Chao TC, Lo YF, Chen SC, Chen MF. Color Doppler ultrasound in benign and malignant breast tumors. Breast Cancer Res Treat 1999;57:193-199.
19. Mesaki K, Hisa N, Kubota K, Hisa N, Ogawa Y, Yoshida S. Differentiating benign and malignant breast tumours using Doppler spectral parameters including acceleration time index. Oncol Rep 2003;10:945-950.