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# Neovascularity patterns in breast carcinoma: Correlation of Doppler ultrasound features with sonographic tumour morphology

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ORIGINAL ARTICLE

# Neovascularity Patterns in Breast Carcinoma: Correlation of Doppler Ultrasound Features with Sonographic Tumour Morphology

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## ABSTRACT

**Objective**: To determine the association and correlation between morphologic features of breast cancer on gray scale ultrasound, and vascularity patterns and indices on color and spectral Doppler ultrasound.

**Study Design**: Cross-sectional, analytical study.

**Place and Duration of Study**: Department of Radiology, Dow University of Health Sciences and Civil Hospital, Karachi, from August 2006 to June 2007.

**Methodology:** Fifty adult female patients with histopathological proven breast cancer underwent ultrasound for evaluation of morphologic features on gray scale mode; vascularity patterns on color Doppler scan and flow indices measurement on spectral Doppler ultrasound. Regression analysis was conducted to determine correlation between the variables and associations of vascularity patterns.

**Results:** The 50 studied patients had predominantly solid tumour in 46 (92%) with depth to width ratio of > 1 in 37 (76%). The mean tumour size was 3.6 ± 1.34 cm, with irregular margins in 41 (82%), posterior shadowing in 43 (86%) and calcifications in 27 (54%). Type 3 vascularity (multiple peripheral vessels) was the most frequent pattern (n=21, 42%) that showed a positive correlation with solid tumours ($r=0.7$, $p < 0.001$). Low resistance spectral waveform was seen in 44 (88%) cases. The average size was 3.69 cm in vascular and 3.1 cm in avascular tumours. Mean resistive index (RI) was 0.67. Mean pulsatility index (PI) was 1.1. RI was significantly high in cystic tumours (mean=0.8, $p < 0.001$) and significantly low in tumours measuring less than 2 cm (RI=0.18, $p < 0.001$).

**Conclusion**: In this study, multiple peripheral vessels with low resistance flow was the pattern most significantly associated with all appearance of focal breast cancer. Apart from a positive correlation with solid tumours, markedly high RI in cystic tumours and markedly low RI in tumours less than 2 cm, there was no consistent correlation trend difference between Doppler findings and tumour size. Histopathology, therefore, remains the main modality to evalute the tumour type and characteristics.

**Key words:** *Breast carcinoma. Ultrasound. Morphology. Vascularity. Doppler. Resistive index (RI). Pulsatility index (PI).*

## INTRODUCTION

Breast cancer is the most common malignancy among the females and the leading cause of cancer related-deaths among middle aged women.[1] It is the most frequently recorded female malignancy in Pakistan as well, being responsible for a third of all cancers.[2,3]

Early diagnosis remains the key for improving survival by identifying smaller lesions that have a potential for more aggressive biological behaviour in terms of metastasis and spread.[4] This is even more important in the local settings since there is no existing breast cancer-related mass screening program in Pakistan and public awareness is minimal.[5]

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An important determinant regarding aggressiveness and survival for any cancer including breast cancer is the vascularity status.[6] The tumoural vascularity is the neovascularity or angiogenesis which is the emergence of new vessels in a tumour that develop randomly without any pre-determined pattern and lack smooth muscles in the wall that facilitates feeding tumours.[8,9]

Considerable experimental evidence has shown tumour growth to be dependent upon vascularity and evaluation of latter is important for deciding treatment options once a particular mass is diagnosed to be malignant.[9,10]

Histopathological determination of vascularity status of breast cancer by determining micro-vascular density (MVD) is an invasive approach. However, Doppler sonography has been shown to correlate convincingly with the sonographically visible and measurable tumour vascularity and MVD determined by immuno-histochemical analysis.[8] This vascularity is known to correlate with tumour dimension and necrosis within tumour.[9,11] Measuring the flow indices can also help in flow characterization.[9]

Many researchers have described varying patterns of tumour vascularity with overlapping descriptions.[8-11] A simpler description is given by Bhargva *et al.* for vascularity patterns of superficial masses and nodules- as being avascular (type-1), single vessel (type-2), multiple peripheral vessels (type-3) and multiple peripheral and intratumoural vessels (type-4) in a mass.[12] These patterns have not been evaluated before; for a breast mass in these simplified types.

Image analysis of sonographic features of malignant breast lumps have been studied in local setting but local data on vascularity patterns of breast cancer is lacking. Moreover, no research has yet been done on correlating different sonomorphologic features of malignant breast masses with Doppler vascularity. Determining such an association may help to identify those sonomorphologic features of breast cancer on gray scale ultrasound that may give a clue to the presence of malignant neovascularity and, therefore, possibly aggressive biological behaviour of a tumour.

The aim of this study was to determine if there was a relation between the sonomorphologic features of a focal malignant breast mass seen on gray scale ultrasound, and the vascularity patterns as visible and measurable on unenhanced color and spectral Doppler sonography.

## METHODOLOGY

This cross-sectional, analytical study was conducted from August 2006 to June 2007 at the Department of Radiology, Dow University of Health Sciences and Civil Hospital, Karachi with input from the Department of General Surgery. A total of 50 patients were inducted by purposive non-randomized sampling. Inclusion criterions were adult female patients with unoperated focal solid breast mass and histopathological confirmation of malignancy. Patient with generalized pathology, inflammatory carcinoma, multifocal masses, histologically proven benign mass, male breast cancer cases and those female breast cancers with history of receiving any kind or combination of breast surgery, previous chemotherapy or radiotherapy, were excluded.

Demographic data was collected regarding identification, age, address, family history, marital status, menstrual, obstetrical and lactational history as applicable, possible risk factors including oral contraceptive pills (OCs) intake, and details of presenting complaints and physical examination. Mammographic reports were also considered where available.

After informed consent, breast ultrasound (U/S) was done by micro-convex linear array probe of 11.5 MHz on Toshiba Nemio-17. Gray scale U/S and color and spectral Doppler scan was conducted by the authors. Gray scale sonomorphologic features were defined as size in cm (measured from defined margin in the largest dimension, including the echogenic rim around the lesion, when present), depth to width (D/W) ratio, consistency (solid or cystic, the latter including predominantly necrotic tumours), margins, regularity, sonographically visible calcifications and diffuse posterior acoustic shadowing representing scirrhous or high density lesions in the absence of calcifications.

Doppler scan was done by adjusting the size of color box to include the mass as well as adjacent normal breast tissue. Vascularity pattern was divided in to either of the four types defined earlier.[12] Pulsatility index (PI) and resistive index (RI) were determined for the largest calibre lesional vessel showing arterial pattern using standard formulae and in-built measurement and considering the lowest value on two averaged waveforms on spectral analysis.[6]

Descriptive and inferential statistics were applied using SPSS version 12. Frequency, mean and standard deviations were determined for age and other demographic variables. Regression analysis was carried out using Spearman test for vascularity patterns and indices with sonomorphology. Pearson correlation test was used for correlation between tumour size and flow indices. Parameters relating to vascularity (i.e. pattern and flow indices) were considered dependent variables. Two tailed significance was also determined using Pearson chi square test and Fisher exact test as applicable according to number of cases. Significance was considered at 'p' less than 0.05. A perfect correlation was considered at r=1, a strong correlation at $r > 0.5$ and $< 01$, weak correlation at $r \leq 0.5$ with + values indicating positive and negative values indicating negative correlation.

## RESULTS

There were a total of 50 cases with mean age of 41.5 ± 9.6 years ranging from 26 to 70 years. Maximum cases (n=19, 38%) belonged to 36-45 years of age while 16 (32%) aged 25-35 years.

Positive family history was found in 31 (62%); 35 (70%) had menarche at under 12 years of age; 47 (94%) were married with 35 (70%) having more than 3 children and 33 (66%) had lactated for over one year. Intake of oral contraceptive was stated in 20 (40%).

Clinically, 35 (70%) had tumour size T2 (2-5 cm), 11 (22%) had T3 (> 5 cm) and 04 (8%) had T1 (< 2 cm). Histopathologically there were 22 (44%) infiltrating ductal carcinoma, 11 (22%) ductal carcinoma-*in-situ*, 4 (8%) medullary, 6 (12%) papillary, 3 (6%) lobular carcinoma-*in-situ*, 2 (4%) Pagets disease and 01 (02%) each of colloidal and infiltrative lobular carcinoma cases.

**Table I**: Tumour sonomorphology and patterns of flow.

| Morphological features | Flow pattern | | | | Statistical value | |
|---|---|---|---|---|---|---|
| | Type-I | Type-II | Type-III | Type-IV | r-value | Significance |
| Consistency | | | | | | |
| Soldi (46) | 3 | 15 | 19 | 9 | 0.7 | < 0.001 |
| Cystic (04) | 0 | 0 | 3 | 1 | 1.00 | < 0.001 |
| Margins | | | | | | |
| Regular (09) | 1 | 0 | 5 | 3 | 0.91 | < 0.001 |
| Irregular (41) | 2 | 15 | 17 | 7 | 1.00 | < 0.001 |
| Calcification | | | | | | |
| Present (27) | 3 | 7 | 11 | 6 | 0.99 | < 0.001 |
| Absent (23) | 0 | 8 | 11 | 4 | 0.93 | < 0.001 |
| Post shadowing | | | | | | |
| Present (43) | 3 | 12 | 20 | 8 | 0.965 | < 0.001 |
| Absent (7) | 0 | 3 | 2 | 2 | 0.992 | < 0.001 |
| Depth/width ratio | | | | | | |
| < 1 (13) | 1 | 4 | 7 | 1 | 0.993 | < 0.001 |
| > 1 (37) | 2 | 11 | 15 | 9 | 0.996 | < 0.001 |
| Tumour size | | | | | | |
| < 1.9 cm | 0 | 2 | 2 | 0 | 1.00 | < 0.001 |
| 02.0 - 4.9 cm | 2 | 12 | 13 | 6 | 1.00 | < 0.001 |
| 05.0 - 10.0 cm | 1 | 1 | 7 | 4 | 1.00 | < 0.001 |

**Table II**: Morphology versus flow indices.

| Morphology | Mean RI ± SD | Mean PI ± SD | r-value | Significance |
|---|---|---|---|---|
| Consistency | | | | |
| Solid (46) | 0.61 ± 0.26 | 0.96 ± 0.45 | 0.964 | < 0.001* |
| Cystic (04) | 0.80 ± 0.34 | 1.31 ± 0.57 | 1.00 | < 0.001* |
| Margins | | | | |
| Regular (9) | 0.6125 ± 0.29 | 0.985 ± 0.5 | 0.994 | < 0.001* |
| Irregular (41) | 0.627 ± 0.236 | 0.955 ± 0.43 | 0.959 | < 0.001* |
| Calcification | | | | |
| Present (27) | 0.60 ± 0.27 | 0.95 ± 0.45 | 0.99 | < 0.001* |
| Absent (23) | 0.65 ± 0.22 | 1.01 ± 0.40 | 0.934 | < 0.001* |
| Post shadowing | | | | |
| Present (43) | 0.62 ± 0.24 | 0.98 ± 0.42 | 0.965 | < 0.001* |
| Absent (07) | 0.61 ± 0.28 | 0.98 ± 0.49 | 0.992 | < 0.001* |
| Depth/Width ratio | | | | |
| < 1 (9) | 0.61 ± 0.24 | 0.98 ± 0.43 | 0.994 | < 0.001* |
| > 1 (41) | 0.62 ± 0.25 | 0.95 ± 0.40 | 0.965 | < 0.001* |
| Tumour size | | | | |
| < 1.9 cm | 0.18 ± 0.3 | 0.24 ± 0.4 | 1.00 | < 0.001* |
| 02.0 - 4.9 cm | 0.64 ± 0.2 | 1.00 ± 0.38 | 0.95 | < 0.001* |
| 05.0 - 10.0 cm | 0.69 ± 0.23 | 1.12 ± 0.38 | 0.997 | < 0.001* |

** Significant association.*

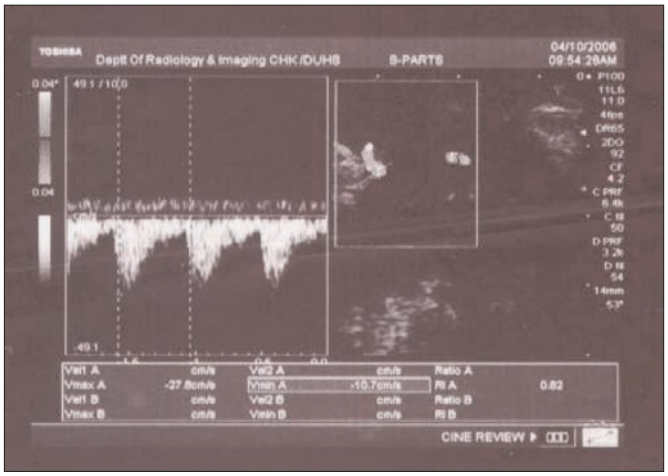


**Figure 1:** A solid malignant lesion showing type 3 vascularity on Doppler ultrasound with moderate resistance flow.

The morphological features showed that majority of the lesions had vascularity of type-3 (Figure I, Table I) irrespective of consistency. Significant associations of type-3 vascularity with solid tumours, irregular margins, posterior shadowing, D/W ratio > 1 and tumour size of 2-5 cm, a strong positive correlation trend was found with type 3 (Table I).

Same trend was observed with the Doppler indices which had a significant association and strong to perfect correlation with many of the morphologic features (Table II). The overall mean PI was 1.1 and RI was 0.67. Low resistance arterial spectral waveform was seen in 44 (88%) cases. All tumours measuring 2 cm or more in size showed RI of around 0.6 as shown in Table II. It was significantly higher in cystic tumours (mean RI=0.8, $p < 0.001$) and significantly low in tumours less than 2 cm (mean RI=0.18, $p < 0.001$).

## DISCUSSION

Approximately one in every 9 Pakistani women is likely to suffer from breast cancer, which is one of the highest incidence rates in Asia.[5] Triple assessment by physical examination, mammography and biopsy remains the mainstay of initial diagnosis.[1] Vascularity assessment that sustain a tumour and predicts survival then needs to be evaluated for management options. This study explored features using a non-invasive technique that is Doppler sonography which shows vascularity patterns and can even measure flow indices. Doppler is known to have good correlation with MVD shown to be better than another minimally invasive, low radiation technique of $^{99m}$Tc MIBI scintimammography.[15]

The salient findings of this study were predominant involvement of middle aged group, a mean tumour size of 3.6 cm (T2 according to TNM classification), most tumours being solid and vascular with multiple peripheral vessels having low resistance arterial flow; a mean RI of 0.6 which increased significantly for cystic or necrotic and decreased markedly for small sized T 1 tumours. More importantly it dispelled one myth that Doppler scan always predict a malignant mass.

In this study, the mean age of breast cancer patients was 41.5 years as compare to 43.6 years age found by Haider *et al.*[16] Majority (92%) of the cases had tumour size greater than 2 cm (T2 and beyond) with mean size of 3.6 cm. This is in contrast with Western studies which have shown majority cases to be less than 2 cm.[10] This probably reflects late presentation in local population as a result of lack of awareness regarding self-examination and the non-existent population-based breast cancer screening programs.

Breast cancer is amenable to ultrasound examination due to its superficial location and Doppler evaluation provides a near ideal *in-vivo* evaluation of tumour vascularity features.[8] The non-significant correlation of tumour size with vascularity has been found by Western researchers but local data was lacking as yet before this study.[17,18]

In the present study, 88% masses were vascular while Schoenberger *et al.* found 100% malignant masses to be vascular.[19,20] Hypervascularity in terms of multiple peripheral vascularity, as found in this study, has been identified as a frequent feature by other researchers as well.[6,9,10] Kubek *et al.* have even described a peripheral rim of branching vessels as a sure and common sign of malignancy on color and pulsed Doppler U/S.[21] In this study multiple peripheral vessels around tumour was the commonest vascularity pattern. However, many tumours were avascular or even sparsely vascular. This dispels the myth that a malignant mass is always highly vascular. This may be true for solid but not cystic tumours.

The resistance indices selected in this study was resistive index (RI) and Pulsatility index (PI). Their lowest values were selected on the assumption in congruity with Takayuki *et al.* as the vessels with low resistance flow are likely to be the main tumour feeder.[6]

In this study, the mean RI was 0.64 which was lowering comparable to Hollerwerger *et al.* who found RI to be > 0.8.[22] Mean PI in this study was 1.1. However, much overlap has been reported for the cutoff values of these indices. Bhargava *et al.* have mentioned PI of > 1.4 and RI of > 0.8 as the cutoff point for malignancy.[12] Peter-Engle *et al.* has suggested RI cutoff at > 0.70.[22] However, Mehta *et al.* have refuted RI and PI as being important parameters due to variable and conflicting reports.[9]

Cassano *et al.* pointed out that invasive tumours without central necrosis were more likely to be widely vascular.[11] This collaborates the present findings of solid tumours being more abundantly vascular. However, the small number of cystic tumours that included predominantly necrotic tumours as well also had multiple peripheral vessels. The solid tumours that turned out to be avascular were mostly Paget's disease, medullary and lobular carcinoma.

The finding of low PI in small sized tumours is also interesting. It may be that these tumours were developing neovascularity at the time of detection since angiogenesis is a pre-requisite for tumour growth.[23]

The limitations of this study relatively include smaller number of patients; lack of correlation with MVD on histopathology and immunohistochemistry; and non-consideration of nodal, lymphovascular and distant metastasis.

However, budgetary liaison and time constraints for completion of study in a specified period were the main reasons behind it. Still, it is one of the earliest local data to give details about breast cancer sonomorphologic features frequency and distribution, and their Doppler characteristics details.

## CONCLUSION

In this studied group of breast cancer patients, multiple peripheral vessels with low resistance flow was the vascularity pattern most significantly associated with all ultrasound based morphologic appearance of focal breast cancer. There was a positive correlation between solid tumours and above mentioned vascularity pattern. Perfect correlation was found with cystic tumours and irregular margins. The mean RI was 0.6 which was markedly high (0.8) in cystic or necrotic tumours and markedly low (0.18) in tumours less than 2 cm in size. However, there was no consistent correlation difference trend between Doppler findings and tumour size.

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