

DOPPLER INDICES EVALUATION IN MALIGNANT BREAST LESIONS-REVIEW ARTICLE

ABSTRACT

The incidence of breast malignancy has displayed a rapid rise in recent times. It is one of the most common malignancies found in women. Women should be educated and made aware about self breast examination in order to detect malignancies at an early stage so that the prognosis can be improved. Breast pathologies can be classified into malignant and benign ones on the basis of signs and symptoms and by ultrasonography but can be confirmed on histopathology which remains the gold standard. Breast ultrasonography is the most common non ionising radiological investigation used to assess breast lesions especially in women with dense or painful breasts. Breast carcinomas appear irregularly shaped hypoechoic lesions with non circumscribed margins but these features can rarely be manifested by benign lesions as well. Recent introduction of doppler ultrasound has led to an increase in the sensitivity of detecting breast carcinoma since most of the breast malignancies are hypervascular and they show high resistivity index on spectral analysis. Angiogenesis in malignant lesions lead to formation of structurally abnormal and tortuous vessels with increased resistive index. Several studies on doppler analysis of breast malignancies have shown Doppler ultrasound to be a safe and effective modality showing acceptable diagnostic accuracy for noninvasive characterization of malignant breast lesions. Therefore, it can be employed as an alternative to histopathology in patients who present with breast lesions.

Keywords: Malignancy, Breast, Doppler, Lesions, Ultrasound

INTRODUCTION:

Today, breast cancer is amongst one of the leading cause cancer in world (1). Breast tissue is made up of tubules and lobules which are surrounded by thin fibrous tissues. Alteration in the components of breast tissue leads to breast pathologies. Intraductal breast mass is the most commonly seen breast carcinoma and it can be solitary or can be multiple in number because they are intraluminal lesions which grow in lactiferous ducts. These ductal carcinomas are usually close to the subareolar region but can be found elsewhere. The patient may feel a small painless lump or be aware of a clear or bloody discharge from the nipple. (2)

The addition of mammography to breast screening tests increased the number of diagnoses of breast cancer. Breast ultrasonography (US) for women with compressed breast tissue resulted in the diagnosis of undetected breast cancer in mammography at the same time. (3) Breast ultrasound is a very useful tool for diagnosing breast carcinomas. Ultrasound of the breast can be classified as a screening or diagnostic test. The goal of screening is to detect breast abnormalities in a large area of undiagnosed patients, and the purpose of diagnostic ultrasound is to perform tests that focus on diagnosing a symptom or symptom, such as mild discomfort, or abnormalities noted in previous imaging conditions (4). The use of ultrasound has shown an amazing promise

of differentiating the benign from malignant lesions. Recently introduced, the sonographic BI-RADS lexicon has demonstrated its usefulness in distinguishing risk from solid masses (5)

Harmonic imaging, compound imaging, power Doppler, high-frequency transducers, and, the more recent technique of elastography and 3D US are examples of advances in US technology. Folkman originally proposed the link between angiogenesis (the creation of new blood vessels) and cancer in 1971. Hypoxia occurs when active cancer cells require more oxygen and nutrients than most regular vasculature can provide. To maintain the tumor's homeostasis, this hypoxic environment induces the development of new vessels that flow from existing blood vessels to the tumour. (7)

Color Doppler sonography is a valuable tool for distinguishing cystic ulcers from their malignant counterparts, detecting benign tumours from malignant lesions, identifying vascular abnormalities, and assessing tumour therapy response. Although Doppler sonography is now thought to be a useful component in grayscale ultrasound for distinguishing solid and cystic lesions, its precise role in distinguishing malignant from benign lesions has yet to be discovered. Many new research are being carried out utilising diverse models to determine neovascularity, which has demonstrated its promising role. However, more research is needed to confirm their efficacy in distinguishing the danger from malignant tumours.. (4)

The CD's use in classifying breast lesions has been investigated in a number of studies. The discovery of vascularization in the lesion was the first feature of Doppler utilised to discriminate between a malignant and non-malignant tumour. According to Cosgrove et al. (1993), blood vessels were seen in 99 percent of malignant lesions, but only 3 percent of benign lesions had signals on doppler Doppler symptoms. Blood flow was detected in benign lesions as well, thanks to current technological advancements (Birdwell et al. 1997). The pattern of vascular distribution in the lesion was another criterion utilised to distinguish malignant from benign lesions. The presence of penetrating arteries was used to diagnosis malignant lesions, while peripheral vascularization was used to diagnose benign lesions. As a result of developments in CD technologies, diagnostic criteria have shifted. (8)

DS is a fast, inexpensive, and non-invasive method of diagnosing vascularization. DS can be very helpful for people with asthma due to their surface area, which is why many studies are being done to test the effectiveness of this method in diagnosing malignant and malignant lesions and predicting prognosis. Doppler indices such as resistivity (RI)and pulsatility index (PI) are higher in cases of malignant tissue . The reason may be an unusual vessel structure , turbulent flow , increased vascularity , arterio-venous fistulas for malignant tumors (9)

Although sonography has historically been used to diagnose cystic lesions in solid wounds, there has been a growing interest in using sonography to differentiate the risk from solid tumors and to avoid biopsies due to its ability to identify lesions with traumatic traits. Sensitivity to sonography has been found to be higher than mammography especially in the premenstrual breast. Today, sonography plays a key role in guiding interventions such as needle aspiration, core needle biopsy and local pre-biopsy and needle

DISCUSSION:

Breast cancer is a heterogeneous disease i.e. it has several underlying causes that result in its manifestation. It is one of the most commonly seen cancers among women. Every year, more than 1.2 million women worldwide are diagnosed with breast cancer, according to WHO statistics . It can have genetic as well as non genetic factors leading to metaplasia of normal cells turning them malignant.

On Ultrasonography , breast cancer appears as a hypoechoic lesion which is irregularly shaped with non circumscribed angulated/lobulated/spiculated margins. However , its appearance can differ, and can even be similar to that of benign tumours. The spiculated margins are due to the surrounding desmoplastic reaction which involves the growth of fibrous and dense tissue at the site of tumour growth. (10) Malignant tumors secrete Pro-angiogenic factors, which accelerates vascularisation leading to formation of new blood vessels. Neoangiogenetic vessels are irregular and tortuous in course having variable calibre , and they create reticular networks leading to formation of arteriovenous shunts and dichotomous branching, which distinguishes them from native vessels (11)

Tariq, Mahjabeen, et al (12) found an increase in the efficacy of spectral doppler ultrasound as a method of choice for evaluating breast masses in patients without the necessity for biopsy in a study conducted on 100 patients in 2010..

considered lesions as benign when the range for RI and PI were 0.32 to 0.62 and 0.7 to 1.15 respectively and malignant when the RI and PI were 0.7 to 1 and 1.7 to 3.7 respectively. The study showed both RI and PI having high sensitivity i.e 94.2% and 96.1% , high NPV of 93.4% and 95.5% respectively . Specificity was found to be 89.5% for RI and 89.5% for PI whereas PPV was 90.7% and 90.9% for RI and PI respectively .

Stanzani, Daniela, et al (11) conducted another investigation in 2014 to see if specific features of vascularity of breast masses using color and duplex Doppler will add to the analysis done by gray-scale sonography and support the Ultrasound lexicon of BIRADS categorization. They studied 70 solid lesions and found a link between vascularity and spectral index and histology. Hypervascularity in lesions with tortuous , penetrating arteries and a RI of 0.73 were found to be strongly predictive of malignancy (p0.001) with a sensitivity of 76 percent and specificity of 71 percent. This above mentioned cut-off value of RI allowed for considerable (p<0.001) differentiation between malignant and benign ones. The mean RI value of benign lesions was 0.480 with 14 (31.1%) having a RI value of 0.73 (p < 0.001).

Davoudi, Yasmin, et al.(13) sought to examine the utility of spectral doppler and color doppler ultrasound in analyzing solid breast masses in 38 cases in 2014 and performed colour doppler for each patient and evaluated the RI values and compared with tissue biopsies They discovered that breast malignancies had additional blood vessels in comparision benign breast lesions. 97.4% of breast malignancies were found to have Blood vessels in comparision to just 35% in benign pathologies .In benign and malignant lesions, the mean RI values were 0.65 +/- 0.065 (range, 0.52to0.89) and 0.71 +/-0.093 (range, 0.57to0.75), respectively. The change was statistically significant but not quite (p Z 0.061). This research yielded a RI value of 0.625 as a threshold. The sensitivity to predict malignancy was 88 percent whereas the specificity was just 57% and

based on this number. They came to the conclusion that the most essential marker in Color Doppler ultrasound for predicting possibility of cancer incase of a breast tumour is hypervascularity. However, it appears that using RI alone to distinguish between malignant and benign breast tumours is ineffective. The gold standard for diagnosing the kind of breast nodules is still pathological evidence.

In 2015, Amany Elkharbotly et al (14) did a study in 60 patients to assess the diagnostic yield of Color Doppler for distinguishing breast lesions, and showed that it was comparable to the gold standard histological analysis. The researchers discovered that 0.56 ± 0.12 was the mean RI value for benign lesions, with a range falling in between 0.44–0.97, and that malignant lesions had a mean RI of 0.86 ± 0.18 , with a range of 0.5–1.2 showing a with statistical significance ($Z = 3.421$, $p = 0.001$). Considering a RI cut off point of 0.85 for discriminating malignant from benign breast pathologies, the sensitivity rate turned out to be 77.8% with a specificity rate of 78.6% However the positive predictive value was 60.9 percent, whereas it has a better negative predictive value of 89.2%, and the diagnostic accuracy is 78.3%.

Gupta, Kanika, et al (15) in 2017 carried out a prospective study to evaluate the usefulness of colour Doppler and spectral Doppler ultrasound in distinguishing malignant from benign lesions and determining malignancy predictive value Color and spectral doppler were used to evaluate 173 solid masses, and the results were compared to FNAC. When comparing benign and malignant lesions, the mean RI was significantly greater for malignant tumours.. The specificity was 57% and sensitivity was 88% for diagnosing and differentiating lesions when the threshold value was set at 0.7. The study concluded that spectral color doppler is an useful diagnostic tool an dprovides additional information needed to categorise breast masses on US.

In a study published in 2018, Keshavarz, Elham, and colleagues (16) looked at the diagnostic accuracy of spectral indices on Doppler ultrasound in 100 patients for discriminating malignant from benign lesions, and showed that RI and PI had excellent diagnostic accuracy since malignant lesions had high values.

Dr. Pearly Stephen and colleagues (17) did a study to determine the role and importance of Resistive Index and patterns of vasculairsation obtained with Color Doppler and spectral doppler Ultrasound (CDUS) in differing malignant breast patholgies from benign ones, as well as to compare and correlate imaging and doppler findings with tissue diagnosis. They discovered that malignant breast lesions have significantly elevated values of $RI > 0.73$, as well as the existence of penetrating vessels, radially oriented and displaying chaotic vascularity. When the RI is between 0.66 and 0.73, with peripheral net pattern of vascularisation around the margins of tumor, suggested typically benign lesions. In ways like this, it was easy to distinguish malignant lesions from benign ones and also one could categorise indeterminate lesions into either of the two. This enables the distinction between malignant and benign breast pathologies to be made, as well as categorise ambiguous lesions into one of the two categories. Color Doppler sonography, they added, is an ideal imaging modality for accurate diagnosis of breast lesions and can be utilised in conjunction with primary imaging modalities such as mammography and greyscale imaging.. Some of the traits were statistically examined to see what influence they played in better assessing breast tumours. It's based on the fact that, when compared to the

normal breast parenchyma, most malignant lesions have greater neovascularization than benign lesions.

50 patients with focal lesions in breast were evaluated on Spectral color doppler and correlated with gold diagnosis of histopathology by Dr. Jyoti Reddy et al (18) in 2019. Results showed that there was a significant statistical difference ($P < 0.0001$) in the spectral indices i.e. RI and PI of malignant and benign lesions. The mean RI of benign and malignant lesions turned out to be 0.60 ± 0.06 and 0.81 ± 0.07 whereas that of PI was 0.82 ± 0.10 for benign and 1.62 ± 0.38 for malignant lesions. According to the findings, ultrasound with Doppler may reliably distinguish malignant lesions from benign ones, obviating the need for invasive investigations in patients.

Sabba Sachi Sarkar (19), in 2019 revealed in their study that the difference in mean RI for malignant and benign lesion was significant ($p < 0.05$).

A cross sectional study was done by **Parveen, Ishrat, et al. (20)** in 2020 to find the accuracy of RI in predicting malignancy and comparing with its histopathological diagnosis. They sampled 150 patients and analysed the vascularity and spectral RI. They found a sensitivity of 92.4% with PPV of 90.12%, specificity and NPV of 88.77% and 91.3%. The Diagnostic accuracy of Spectral Doppler Ultrasound from this study came out 90.67%. They concluded that neoangiogenesis in malignancy led to abnormally structured tortuous vessel which had increased resistance. They also found that Doppler ultrasound as a modality is effective and safe and had a good diagnostic accuracy for characterising malignant breast masses in a non-invasive manner. The study also suggested that Spectral Doppler ultrasound should be applied as an alternative diagnostic method to histopathology in breast lesion-containing patients.

Al Hialy. et al (21) did a study in 2020 which aimed to find the efficacy of Color Doppler Ultrasound in diagnosing cancers of breast amongst the palpable and non-palpable in 875 women. Presence of vascularity, degree of vascularisation, spectral indices such as RI and PI were analysed in order to find its role in differentiating malignant lesions from benign. Malignant lesions had increased vascularity in comparison to benign breast pathologies and the Doppler spectral indices were significantly higher for malignant lesions in comparison to benign lesions with a significant statistical difference ($p < 0.001$). The mean Resistivity index for benign lesions were 0.67 and 0.719 for malignant ones. The probability value of $p = 0.013$.

Significance of color doppler ultrasound and RI was analysed by Waqar, Sehrish, et al (22) in 2021 in 38 solid lesions. Spectral Doppler indices were compared with pathological results. Their study found that benign lesions were less vascular (35%) as compared to malignant ones (94%). The mean RI of malignant and benign lesions were 0.70 ± 0.092 and 0.64 ± 0.064 respectively. They concluded that Resistive index and vascularity play an important role in differentiating malignancy from benign lesions.

JUKURI, NAGANARASIMHARAJU, et al (23) in 2021 did a prospective cohort study to establish the efficiency of Spectral Color Doppler Indices for predicting the chances of malignancy in case of BI-RADS 3 Lesions. 257 patients were sampled and spectral Doppler indices such as RI and PI were evaluated and then compared with gold diagnosis i.e. histopathology.

On spectral Doppler analysis, high RI and PI were good predictors of malignancy. The cut off of 0.6 was considered to have a good sensitivity of 87.5% and 85.8% specificity, whereas when the RI was set at a cut off of 0.8 for malignancy, the specificity increased but the sensitivity decreased to 62.5%. Similar result was seen with PI when the cut off was 0.9 for malignancy, it had a specificity of 85% and sensitivity at 87% whereas when PI was 1.6 or above for malignancy, the specificity increased but sensitivity decreased. They concluded that spectral color doppler is a reliable technique in predicting malignancy of BI-RADS 3 breast masses. Few of the related studies on breast malignancies were reviewed(24-27).

CONCLUSION:

In conclusion, Spectral doppler Ultrasound can differentiate malignant breast lesions from benign to great extent. This additional technique has a good potential ability in altering the handling of cases in which a biopsy may be recommended

REFERENCES:

- 1) Gokhale S. Ultrasound characterization of breast masses. *The Indian journal of radiology & imaging*. 2009 Aug;19(3):242.
- 2) El Sheikh H, Almetaher HA, Abdalla HS, Shareef MM. Intraductal breast masses: Sonographic and mammographic predictors of malignancy. *The Egyptian Journal of Radiology and Nuclear Medicine*. 2015 Dec 1;46(4):1271-8.
- 3) Izumori A, Takebe K, Sato A. Ultrasound findings and histological features of ductal carcinoma in situ detected by ultrasound examination alone. *Breast Cancer*. 2010 Apr 1;17(2):136-41.
- 4) Ackerman S. Color Doppler sonography: characterizing breast lesions. *Imaging in Medicine*. 2010 Apr 1;2(2):151.
- 5) Blaichman J, Marcus JC, Alsaadi T, El-Khoury M, Meterissian S, Mesurolle B. Sonographic appearance of invasive ductal carcinoma of the breast according to histologic grade. *American Journal of Roentgenology*. 2012 Sep;199(3):W402-8.
- 6) Hooley RJ, Scutt LM, Philpotts LE. Breast ultrasonography: state of the art. *Radiology*. 2013 Sep;268(3):642-59.
- 7) Ibrahim R, Rahmat K, Fadzli F, Rozalli FI, Westerhout CJ, Alli K, Vijayanathan A, Moosa F. Evaluation of solid breast lesions with power Doppler: value of penetrating vessels as a predictor of malignancy. *Singapore medical journal*. 2016 Nov;57(11):634.
- 8) Watanabe T, Kaoku S, Yamaguchi T, Izumori A, Konno S, Okuno T, Tsunoda H, Ban K, Hirokaga K, Sawada T, Ito T. Multicenter prospective study of color Doppler ultrasound for breast masses: Utility of our color Doppler method. *Ultrasound in medicine & biology*. 2019 Jun 1;45(6):1367-79.
- 9) Sirous M, Sirous R, Nejad FK, Rabeie E, Mansouri M. Evaluation of different aspects of power Doppler sonography in differentiating and prognostication of breast masses. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2015 Feb;20(2):133.
- 10) Farooq SM, Robot GC, Murrium SK, Gilani A, Gilani HS, Nazir M, Haider Z. Diagnostic Accuracy of Ultrasonography for Evaluation Solid Breast Lesions—A Systematic Review. *Asian Journal of Allied Health Sciences (AJAHS)*. 2021 Mar 19.

- 11) Stanzani D, Chala LF, Barros ND, Cerri GG, Chammas MC. Can Doppler or contrast-enhanced ultrasound analysis add diagnostically important information about the nature of breast lesions?. *Clinics*. 2014;69:87-92.
- 12) Tariq M, Masood M, Khan TQ, khurshid Ahmad K. Doppler sonography in the diagnosis of breast masses. *PJR*. 2016 Jul 20;20(2).
- 13) Davoudi Y, Borhani B, Rad MP, Matin N. The role of Doppler sonography in distinguishing malignant from benign breast lesions. *Journal of medical ultrasound*. 2014 Jun 1;22(2):92-5.
- 14) Elkarbotly A, Farouk HM. Ultrasound elastography improves differentiation between benign and malignant breast lumps using B-mode ultrasound and color Doppler. *The Egyptian Journal of Radiology and Nuclear Medicine*. 2015 Dec 1;46(4):1231-9.
- 15) Gupta K, Chandra T, Kumaresan M, Venkatesan B, Patil AB. Role of Color Doppler for assessment of malignancy in solid breast masses: a prospective study. *International Journal of Anatomy, Radiology and Surgery*. 2017 Jan;6(1):59-65.
- 16) Keshavarz E, Zare Mehrjardi M, Karimi MA, Valian N, Kalantari M, Valian K. Diagnostic value of spectral Doppler ultrasound in detecting breast malignancies: an original article. *International Journal of Cancer Management*. 2018 Feb 28;11(2).
- 17) Statistical Analysis-Usefulness of Resistive Index and Vascularity patterns to differentiate benign from malignant breast lesions using Color Doppler Ultrasound Authors Dr Pearly Stephen^{1*}, Prof. Dr Adaikkappan
- 18) Reddy J, Khaladkar SM. Evaluation of Focal Breast Lesions on Ultrasound, Color Doppler and Real Time Elastography: A Prospective Study.
- 19) Sarkar SS. To determine role of colour doppler ultrasound in breast lesions. *Journal of Advanced Medical and Dental Sciences Research*. 2020;8(1):203-6.
- 20) Parveen I, Javed K, Elahi B, Nasrullah F, Mahmood R, Aamir MO. Evaluation of breast lesions with Doppler ultrasound: Diagnostic accuracy of resistive index as a predictor of malignancy. *The Professional Medical Journal*. 2020 Apr 10;27(04):825-30.
- 21) Al Hialy HM. Role of Doppler ultrasound study in the diagnosis of breast carcinoma in detected breast Lesion (palpable _ampersand sign impalpable breast mass): A prospective study. *Annals of Tropical Medicine and Public Health*. 2020 Jul;23:23-112.
- 22) Waqar S, Ameer S, Bajwa MA, Bajwa SM, Bajwa GR, Tahir S. SIGNIFICANCE OF DOPPLER RI AND SYSTOLIC PEAK OF BREAST CARCINOMA LESIONS SEEN ON MAMMOGRAPHY. *PAFMJ*. 2021 Feb 25;71(1):319-22.
- 23) JUKURI N, JEHENDRAN MV, THOTAKURA M, NARRA R, REDDY YY. Efficacy of Spectral Doppler Indices in Predicting Malignancy in BI-RADS 3 Breast Lesions: A Prospective Cohort Study. *Journal of Clinical & Diagnostic Research*. 2021 Aug 1;15(8).
- 24) Lamture, Yashwant R., Balaji Salunke, and Shahabuddin Md. "CARCINOMA OF BREAST- A STUDY PROFILE." *JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS* 7, no. 45 (November 5, 2018): 4857–61. <https://doi.org/10.14260/jemds/2018/1082>.
- 25) Dighe, Sajika Pramod, Raju K. Shinde, Sangita Jogdand Shinde, and Anupam Anand. "Review on Assessment of Response of Neo-Adjuvant Chemotherapy in Patients of Carcinoma Breast by High Frequency Ultrasound." *JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS* 9, no. 51 (December 21, 2020): 3873–80. <https://doi.org/10.14260/jemds/2020/849>.

- 26) Jaggi, Ria, Samarth Shukla, Sourya Acharya, and Sunita Vagha. "Utility of TP53 in Breast Carcinoma Immunophenotypes." JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH 14, no. 9 (September 2020). <https://doi.org/10.7860/JCDR/2020/44743.14049>.
- 27) Laddha, Ankita Gajanan, Samarth Shukla, Ravindra P. Kadu, Arvind S. Bhake, Sunita Vagha, and Miheer Jagtap. "Histopathological Types of Benign Proliferative Lesions in Peritumoural Vicinity of Carcinoma Breast." JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH 14, no. 5 (May 2020): EC21–26. <https://doi.org/10.7860/JCDR/2020/43291.13701>.

UNDER PEER REVIEW