DOPPLER ULTRASOUND IN ASSESSMENT OF VASCULAR RESPONSE TO PRIMARY SYSTEMIC CHEMOTHERAPY IN ADVANCED BREAST CANCER.

$Sachin Shetty, # Merwin Paul R
$Associate Professor, Department of Radiology,
Trichy SRM Medical College Hospital and Research Centre, Trichy, Tamil Nadu
#Assistant Professor, Department of Otorhinolaryngology,
Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry.

Corresponding Author: Dr Merwin Paul R
drmerwinpaul@gmail.co

Introduction

Breast cancer is the most commonly occurring cancer in women and the most frequent cause of female cancer death in the world as a whole .Overall, in India, its incidence ranks second, next to that of cervical cancer. But recently it has been found that it is the most common cancer in women in the metropolitan cities.[1,2] The incidence rates are increasing and a higher proportion of newly diagnosed cases are in late stage of disease resulting in an increase in morbidity.

Among those who present with locally advanced disease, the subset of patients who have metastatic disease can only be offered palliative therapy and their 5 year survival rate is dismal (20%).[3] Those who have locally advanced disease but no evidence of systemic metastases, can be treated with an intent to cure. Since in our country 30- 60% of patients present with advanced stage and among them almost half have non metastatic locally advanced disease, disease mortality can be greatly reduced by proper management of these patients.

The treatment options for locally advanced breast cancer include surgery followed by adjuvant chemotherapy and primary systemic chemotherapy (earlier known as neo adjuvant chemotherapy) followed by surgery with or without adjuvant chemotherapy and radiotherapy. Neoadjuvant chemotherapy is the norm now because it can downstage the tumour and convert inoperable tumours into operable ones thereby avoiding morbid, mutilating surgeries.

Assessment of tumour vascularity can be done by Doppler ultrasound and dynamic contrast enhanced MRI. Studies on MRI done in the western world have revealed MRI has a very good accuracy in detecting response. But the expense involved in doing MRI is prohibitive when considered for application to a large number of people especially in a low income country like India. Doppler ultrasound is non invasive and less expensive and is therefore a more practical option in a developing country like ours. This prospective study was done with objective of ascertaining the usefulness of Doppler in predicting the response of LABC to neoadjuvant chemotherapy

Objective

To evaluate Doppler ultrasound parameters in assessment of vascular response to chemotherapy in patients with advanced breast cancer

Methodology

Twenty five patients with advanced breast cancer underwent detailed clinical examination, ultrasonography of breast and axillae, and color and spectral doppler examination at baseline and before every cycle of chemotherapy (FAC regimen) to assess response to chemotherapy. Doppler indices (PSV, EDV, RI and PI) and tumor vascularity (no. of colour signals) were recorded prior to every cycle. Assessment for operability was done at end of 4 cycles and patients were referred to

surgical department for curative surgery. The results of clinical examination, ultrasonography and color doppler were compared with results obtained from histopathology.
All patients received 4 cycles of preoperative FAC chemotherapy once in 21 days as follows:
1. Inj. Cyclophosphamide 500 mg/m2 intravenously on day 1
2. Inj. Doxorubicin 50 mg/m2 intravenously on day1
3. Inj. 5-Fluorouracil 500mg/m2 intravenously on day 1

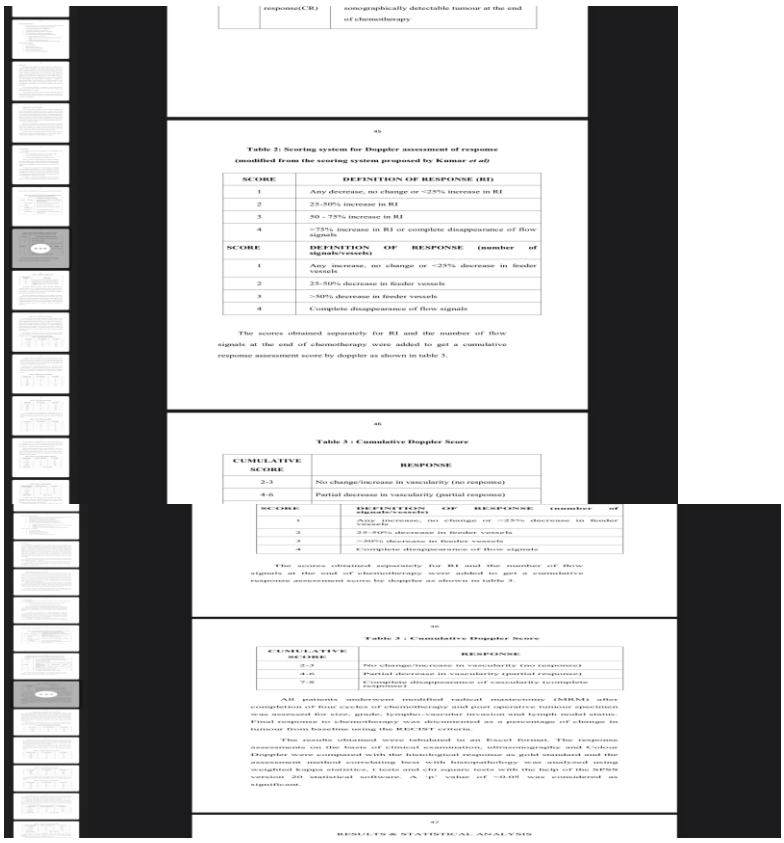

Table 2: Scoring system for Doppler assessment of response (modified from the scoring system proposed by Kumar *et al*)

SCORE	DEFINITION OF RESPONSE (RI)
1	Any decrease, no change or <25% increase in RI
2	25-50% increase in RI
3	50 - 75% increase in RI
4	>75% increase in RI or complete disappearance of flow signals
SCORE	**DEFINITION OF RESPONSE (number of signals/vessels)**
1	Any increase, no change or <25% decrease in feeder vessels
2	25-50% decrease in feeder vessels
3	>50% decrease in feeder vessels
4	Complete disappearance of flow signals

The scores obtained separately for RI and the number of flow signals at the end of chemotherapy were added to get a cumulative response assessment score by doppler as shown in table 3.

Table 3 : Cumulative Doppler Score

CUMULATIVE SCORE	RESPONSE
2-3	No change/increase in vascularity (no response)
4-6	Partial decrease in vascularity (partial response)
7-8	Complete disappearance of vascularity (complete response)

Scoring system for Doppler assessment of response (modified from the scoring system proposed by Kumar et al)

Results
The mean age of our patients was 50.9+ 8.3 years. A baseline doppler examination of the tumour was done at diagnosis and was repeated after each cycle. Majority of the tumours were hypervascular(>5 vessels within 1 cm2 of the tumour). There was no predominant vascular pattern as most tumours had both central and peripheral vascularity.
The most striking feature of the intratumoral vessels was their tortuosity. Their course was marked with multiple sharp turns. This was important because it posed significant difficulty in correction of doppler angle when a doppler spectrum was to be obtained. Though care was taken to obtain all values from relatively straight portions of the vessels and angle correction was done to the best possible extent, the accuracy of doppler angle dependent velocity indices could not be assured owing to the extreme tortuosity. The values of the velocity indices showed a wide variation evidenced by the higher value of standard deviation relative to the mean.

The Doppler values (PSV, EDV, RI and number of flow signals) were tabulated at baseline and after every cycle of chemotherapy. The mean RI at baseline was 0.61 + 0.14 which increased to 0.64+ 0.29 after four cycles. The number of flow signals decreased from 7.2 + 2.2 at baseline to 1.6 + 1.5 at the end of chemotherapy.

The mean PSV measured at baseline was 32.6 + 16.9 cm/sec, and at the end of four cycles it was 18 + 16.3 cm/sec. The mean EDV at baseline was 14.2 ± 16.2 cm/sec which showed decrease to 4.7 ± 6.6cm/secafter 4 cycles of chemotherapy.
The changes in value of Doppler indices obtained at the end of chemotherapy were tabulated. An increase in RI was observed in 61.1% patients whereas 35.2% patients showed a decrease with chemotherapy. Two patients had no change in RI at the end of four cycles of chemotherapy. Compared to the baseline, the number of flow signals decreased in 90% patients, increased in 5.6% patients and remained the same in 3.7% patients. 77.8% patients had a decrease in PSV and 22.2% patients had an increase. In 20.3% patients there was an increase in EDV and in 77.8% patients there was a decrease. One patient had no change in EDV at the end of therapy. At the end of chemotherapy, 35% patients showed an RI score of 1 (<25% increase from baseline), 26% patients showed a score of 2 (25 to 50% increase from baseline), 22% patients showed a score of 3 (50 to 75% increase from baseline) and 17% patients showed a score of 4(>75% increase from baseline). 72% of patients showed >75% decrease in the number of flow signals at the end of chemotherapy (score = 3), whereas only 11% patients showed a complete disappearance of flow signals.
The cumulative Doppler score at the end of therapy was between 2-3 in 15% patients, between 4-6 in 69% patients and 7-8 in 17% patients (16.7%).

Discussion:
Doppler, which is the least expensive method of imaging vascularity, is the only practical option in less well developed countries which are short of the monetary resources required to battle the rising incidence of cancer. The ability to predict the lack of response early not only helps us save the patient from the toxic effects of the ineffective drugs and offer her alternatives for better disease control but also prevent wastage of expensive chemotherapeutic drugs to which some other patient would be sensitive and therefore be benefitted.
It has been proven that the interstitial pressure of the tumour microenvironment is increased due to accumulation of osmotically active macromolecules in the interstitium caused by the increased vascular permeability of tumour vessels.[86] As the tissue oncotic pressure (interstitial pressure) reaches the level of hydrostatic pressure of blood vessels, the tissue perfusion pressure becomes almost nulled as according to Starlings hypothesis,
Tissue perfusion pressure = hydrostatic pressure – tissue oncotic pressure.
Further increases in interstitial pressure cause the tumour blood vessels to collapse by mechanical compression.
It could be construed that this increase in interstitial pressure causing resistance to flow is reflected by resistivity index in Doppler. But this effect could be counter balanced by the arteriovenous shunts which known to be are abundant in the tumour vessels. When AV shunts are present the blood is not exposed to the the resistance of the increased IFP and instead channelized into the low resistance pathway, the veins.
But the tumour microenvironment is very heterogeneous. So a tiny area of increased interstitial pressure could be adjacent to an area of normal interstitial pressure. This could be the reason why there are conflicting reports about the RI values in malignancies.

The vascular response based on the cumulative doppler score at the end of chemotherapy had a good sensitivity, specificity and negative predictive value for prediction of both complete responders (80%, 93.5% and 96%) and non responders (78%, 98% and 96%). It scored far better than clinical examination and B mode ultrasonography. Similar results have been obtained by many of the recently published studies. Kumar et al reported a sensitivity of 66% for doppler on comparison with 45% for clinical examination.Kedar et al and singh et al have also reported good sensitivity of doppler to predict pathological response.
The agreement rate between pathological response and doppler assessment has been found to be very good with a kappa value of 0.77. This surpassed the agreement between HPE and clinical

examination and B mode ultrasonography. This is in concordance with Huber et al who found substantial agreement between doppler and HPE with a kappa value of 0.87.[29] Balu maestro et al have also reported a high correlation between doppler and pathological response.[30]
The accuracy of doppler assessment which reflects the proportion of correct predictions is the highest for doppler at 85%, when compares to 61% for clinical examination and 70% for B mode ultrasonography.
The time and effort involved in any method employed to predict chemotherapeutic response is justified only when it is cost effective and clinically applicable and beneficial in the management of patients.

Conclusion

Doppler ultrasonography has been found to be a non invasive, relatively inexpensive and reproducible method of assessment of response to primary systemic chemotherapy in patients with locally advanced breast cancer. Since it directly visualizes the vessels and assesses tumour vasculature both qualitatively and quantitatively, it is a good method to image neoangiogenessis and vasculogenesis. It not only correlates very well with histopathological response, but also predicts the pathological response with good accuracy as early as after 2 cycles of chemotherapy. Though in this study assessment was done after every cycle, based on the results obtained, we suggest that a pre treatment baseline assessment and an interim assessment at the end of second cycle would suffice for accurate response prediction.

References

1. Preet K. Dhillon, Breast Cancer Factsheet South Asia Network for Chronic Disease, Public Health Foundation of India
2. National Cancer Registry Programme: Consolidated report of the population based cancer registries 1990–1996. Indian Council of Medical Research, New Delhi, 2001
3. Gonzalez-Angulo AM, Hortobagyi GN, Morales-Vasquez F et al. Overview of resistance to systemic therapy in patients with breast cancer. Adv Exp Med Biol. 2007;608:1-22
4. Edge SB, Byrd DR, Compton CC. AJCC TNM Cancer Staging Manual. Springer, Chicago,2010, 7th edition.
5. Singletary SE, Ashley P, Bassett LW, Allred C, Berry D et al. Staging system for breast cancer: revisions for the 6th edition of the AJCC Cancer Staging Manual. Surg Clin N Am 2003, 83:803-819
6. El Saghir NS, Carlson RW, Eniu A, Aziz Z, Hortobagyi GN, Vorobiof D et al. Breast Health Global Initiative Systemic Therapy Focus Group. Locally advanced breast cancer: treatment guideline implementation with particular attention to low- and middle-income countries. Cancer. 2008 Oct 15;113(8 Suppl):2315-24.
7. Early and locally advanced breast cancer: diagnosis and treatment guidelines Published by the National Collaborating Centre for at Velindre NHS Trust, Cardiff, Wales
8. Hortobagyi GN. Comprehensive management of locally advanced breast cancer.Cancer.1990;66:1387–1391.
9. Bonadonna G, Brambilla C, Veronesi U, Ferrari L, Luini A et al. Primary chemotherapy to avoid mastectomy in tumours with diameters of three centimetres or more. Journal of the National Cancer Institute 1990; 82:1539–1545.