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Original Research Article

A Study on Correlation of Nottingham Prognostic Index with Pre-Operative Intratumoral Blood Flow Pattern Assessed by Color Doppler Ultrasonography in Carcinoma Breast

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Abstract: The Nottingham Prognostic Index (NPI), based on invasive tumor size, lymph node stage and histological tumor grade, is a reliable prognostic index used to predict patient survival in both large and small-sized breast cancers. The purpose of the study was to investigate whether pre-operative Color Doppler ultrasonography can be used as a prognostic tool for evaluating the degree of malignancy of breast cancer and hence it attempted to define the correlation of NPI and various other clinicopathological factors with Resistance Index (RI), a measure of pulsatility in neovascularization. RI within the breast tumor correlates significantly with the NPI in breast cancer (p-Value < 0.01). RI of peripheral normal breast tissue does not correlate with NPI and intratumoral RI. Patient's age, size of tumor and hormonal status (ER/PR/HER-2/neu) has no statistically significant correlation with intratumoral RI whereas clinical stage, histological grade and lymph node score of breast cancer correlates significantly with intratumoral RI (p-Value < 0.01). Therefore, Color Doppler ultrasonography with RI as the measuring index can be considered to be a good prognostic marker pre-operatively in determining the degree of malignancy, prognosis as well as the need for neoadjuvant chemotherapy in breast carcinoma and hence, in due course of time, can be expected to be a better non-invasive option than the existing conventional methods which are either costly or invasive or both.

Keywords: Nottingham Prognostic Index, Intratumoral Blood Flow Pattern, Color Doppler Ultrasonography, Carcinoma Breast.

INTRODUCTION:

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20-59 years [1]. It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer-related deaths in women [1]. Presently, 75,000 new cases occur in Indian women every year [7]. Locally advanced breast cancer (LABC) constitutes more than 50 to 70% of the patients presenting for treatment [7].

There is a lot of data on prognostic and predictive factors for breast cancer. A prognostic factor is any measurement available at or before the time of surgery that correlates with disease-free or overall survival in the absence of systemic adjuvant therapy and, as a result, is able to correlate with the natural history of the disease. In contrast, a predictive factor is any measurement associated with response to a given therapy. Prognostic factors may select patients most likely to recur without adjuvant therapy and therefore potentially benefit from therapy and also selects those who are likely to be benefitted from neoadjuvant therapy. In addition, predictive factors may identify the appropriate therapy for an individual patient. There are three main reasons to justify their use. The first is to identify patients with good prognoses for whom adjuvant systemic therapy would not provide a large enough benefit to warrant the risks. The second is to identify patients whose prognoses are poor enough to justify a more aggressive adjuvant approach. And the third is to select patients whose tumors are more or less likely to benefit from different forms of therapy.

A wide variety of morphology-based and molecular-based prognostic factors and tumor markers have been studied as to their potential to predict disease outcome in breast cancer. A partial list of prognostic factors commonly used and under consideration for use in the care of breast cancer patients is as follows:

- Morphology based: Tumor type, Tumor size, Tumor grade (includes mitotic figure count),

Vascular invasion, Resection margin status, Extent of in-situ component, Tumor vessel density (requires immunostatin), Tumor neovascularisation (requires Doppler study) & Lymph node status.

* Non-morphology based "molecular markers": Estrogen & progesterone receptors, Cell proliferation index (immunostatins), S phase by flow or image cytometry, DNA ploidy by flow or image cytometry, Growth factors, Oncogenes (HER-2/neu, myc, ras), Tumor suppressor genes (p53), Proteases (cathepsin D), Cell cycle regulators (cyclins, cyclin-dependent kinases), Plasminogen system (PAI-1, uPAI).

However, the International Consensus Panel of St. Gallen determined the standard prognostic factors of breast cancer as follows: lymph node status, tumor size, histological grade, estrogen/progesterone receptor status (ER/PR) and age [5]. The incidence of regional lymph node metastasis has important prognostic implications in primary operable breast cancer, as does the histological grade.

The Nottingham Prognostic Index (NPI), which is based on invasive tumor size, lymph node stage and histological tumor grade, is a reliable prognostic index used to predict patient survival in both large and small-sized breast cancers [8, 10, 11]. But the NPI is determined based on the size and other parameters of the resected specimen. So the NPI of preoperative cases is difficult to determine.

Some authors have reported that the information obtained by Color Doppler ultrasonography correlates well with surgical stage, tumor grade, tumor invasion and lymph node status in endometrial carcinoma. Recent studies have shown the utility of Color Doppler ultrasonography as a prognostic tool to determine the degree of malignancy of breast cancer based on neovascularization [8]. However, its usefulness for the assessment of high-risk breast cancer patients is still controversial.

The purpose of the present study was to investigate whether pre-operative Color Doppler ultrasonography can be used as a prognostic tool for evaluating the degree of malignancy of breast cancer in individual patients. Therefore, this study attempted to define the correlation of NPI and various other clinicopathological factors with Resistance Index (RI) which is a measure of pulsatility in neovascularization.

MATERIAL AND METHODS:

This was an institution-based, prospective study conducted in Department of Surgery, Medical College, Kolkata, India from January 2011 to June 2012 (18 months). Informed consent was taken from all the patients. The study got clearance from Institutional Ethical Committee. Sample size was 30.

Inclusion Criteria: The following patients were included in the study population:

a) All female patients with operable breast carcinoma who had not received neo-adjuvant chemotherapy and had attended General Surgery OPD or admitted in General Surgery ward of this institution during this tenure were included in this study.

Exclusion Criteria: The following patients were excluded from the study population:

a) Inoperable cases of advanced breast carcinoma.
b) Patients who have already received neoadjuvant chemotherapy.
c) Male patients with breast carcinoma.

All operable cases of female breast carcinoma who had not received neoadjuvant chemotherapy were subjected to a detailed history using a structured questionnaire and examined clinically. Intratumoral blood flow pattern was determined pre-operatively by Color Doppler Ultrasonography. RI value from different parts of the tumor was evaluated and the lowest RI detected within the tumor was noted. The RI value of peripheral breast tissue (assumed to be normal) was also recorded. Baseline investigations of the patients were done which included Hemoglobin, TLC, DLC, ESR, platelet count, Na^+/K^+, random sugar, urea, creatinine, total protein/Albumin/Globulin, A:G ratio, ECG, chest X-ray. TNM (AJCC 7^{th} Edition) staging was done according to clinical findings and available preoperative investigations followed by determination of stage.

After the patients were anesthetically fit for surgery, modified radical mastectomy with axillary lymph node resection was done. Histopathological examination of the specimen was done to evaluate tumor size, histological grade (modified Scarff-Bloom-Richardson system) and lymph node score. All specimens were evaluated without the knowledge of clinical data. Hormone receptors (ER/PR) were also determined by immunohistochemistry method using rabbit monoclonal antibody (ER- clone SP1, PR- clone SP2, Labvision USA) from paraffin-embedded histopathology specimen. ER and PR positivity was defined as the presence of 10% or more positively stained nuclei in ten high-power fields. The intensity of HER-2/neu membrane staining was scored as 0, 1+, 2+ or 3+ (according to standardization of the particular laboratory concerned). Tumors with 2+ or 3+ scores were classified as HER-2/neu positive whereas 0 or 1+ as negative.

NPI was calculated as: NPI=0.2 x tumor size(cm) + grade (I-III) + lymph node score (1-3)

All statistical analyses were performed with SPSS® software version 17.0 for Windows (SPSS, Chicago, IL, USA). The Pearson correlation test was used to examine association between all continuous variables and intratumoral Resistance Index whereas Spearman's Rank Correlation test was applied to check association of all categorical variables with intratumoral Resistance Index. All bivariate analysis was appropriately done and p value < 0.01 was considered significant.

RESULTS:

In this study, 30 female patients of breast cancer were studied.

Descriptive Statistics:

Age:

Mean age was 48.47 years with standard deviation (S.D.) 10.543 years. The range was from 32 to 65 years.

Table 1: Descriptive Statistics of Age.

Age Groups (Years)	Frequency/Number of cases	Percentage
< 35	4	13.3
≥ 35 but < 50	8	26.7
≥ 50	18	60

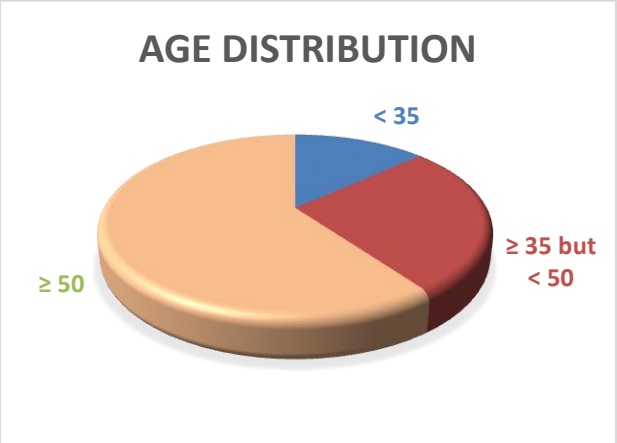

Chart 1: Pie Chart of Age Distribution.

Size of Breast Tumor:

Mean size was 4.52 cm with standard deviation 1.126 cm. the range was from 3 to 6 cm.

Table 2: Descriptive Statistics of Size of Breast Tumor.

Size (cm)	Frequency/Number of cases	Percentage
≤ 2	0	0
>2 but ≤ 5	24	80
> 5	6	20

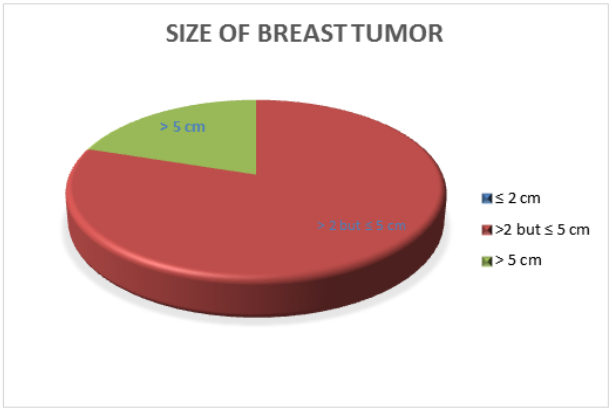

Chart 2: Pie Chart of distribution of Size of Breast Tumor.

Axillary Nodal Status:

Out of 30 patients, 22 had clinically apparent axillary lymphadenopathy (73.3%) among which 12 patients showed less than 3 nodes positive for metastasis on HPE (lymph node score 2) whereas rest 10 showed more than 3 nodes positive on HPE (lymph node score 3). Remaining 8 patients (26.7%) had no clinical axillary lymphadenopathy and also on HPE, they were either negative for metastasis or showed reactive hyperplasia (lymph node score 1).

Table 3: Descriptive Statistics of Lymph Node Score.

Lymph Node Score	Frequency/Number of cases	Percentage
1	8	26.7
2	12	40
3	10	33.3

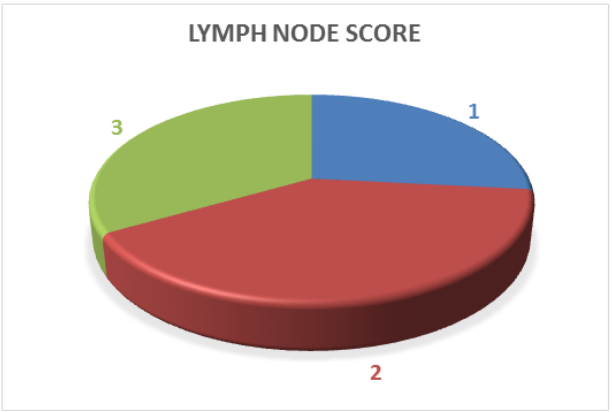

Chart 3: Pie Chart of Lymph Node Score.

Clinical Stage:

All the cases were clinically staged. 2 cases were diagnosed as stage IA (6.7%), 12 cases as stage IIB (40%), 6 cases as stage IIIA (20%) and 10 cases as stage IIIB (33.3%) whereas none of the cases were in stage IB, IIA, IIIC and IV.

Table 4: Descriptive Statistics of Clinical Stage.

Clinical Stage	Frequency/Number of cases	Percentage
IA	2	6.7
IB	0	0
IIA	0	0
IIB	12	40
IIIA	6	20
IIIB	10	33.3
IIIC	0	0
IV	0	0

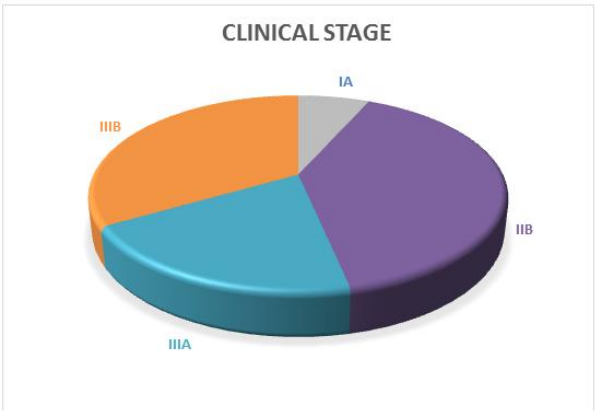

Chart 4: Pie Chart showing distribution of Clinical Stage.

Histological Grade:

The histological grade of the resected specimen was determined by histopathological examination. Out of 30 patients, 12 had grade I tumor (40%), 6 had grade II tumor (20%) and 12 had grade III tumor (40%).

Table 5: Descriptive Statistics of Grade.

Grade	Frequency/Number of cases	Percentage
I	12	40
II	6	20
III	12	40

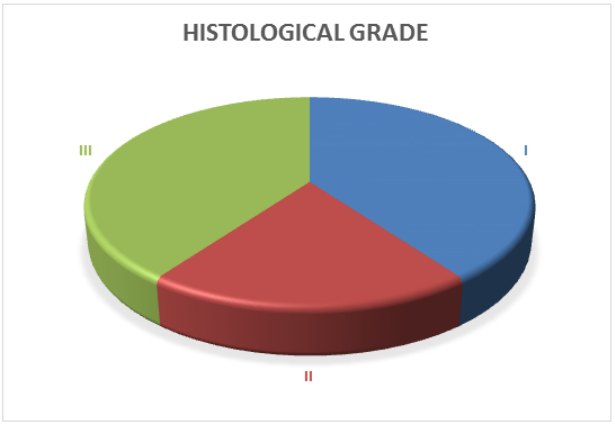

Chart 5: Pie Chart showing distribution of Histological Grade of tumor.

Hormonal Status:

- **Estrogen Receptor status:** Out of 30 patients, 22 were ER positive (73.3%) whereas 8 were ER negative (26.7%).
- **Progesterone Receptor status:** Out of 30 patients, 22 were PR positive (73.3%) whereas 8 were PR negative (26.7%).
- **HER-2/neu Receptor status:** Out of 30 patients, 14 were HER-2/neu positive (46.7%) whereas 16 were HER-2/neu negative (53.3%).

Resistance Index (RI):

- **RI within the breast tumor:**

Table 6: Descriptive Statistics of RI within breast tumor.

No. of cases (N)	Min.	Max.	Range	Mean	Std. Error	S.D.	Variance
30	0.59	0.91	0.32	0.7520	0.01699	0.09309	0.009

- **RI in peripheral normal breast tissue:**

Table 7: Descriptive Statistics of RI in peripheral normal breast tissue.

No. of cases (N)	Min.	Max.	Range	Mean	Std. Error	S.D.	Variance
30	0.58	0.62	0.04	0.6000	0.00263	0.01438	0.000

Nottingham Prognostic Index (NPI):

Table 8: Descriptive Statistics of NPI.

No. of cases (N)	Min.	Max.	Range	Mean	Std. Error	S.D.	Variance
30	3.2	7	3.8	5.208	0.2554	1.399	1.957

Correlation Studies:
Correlation of intratumoral RI with respect to NPI:

Table 9: Correlation of intratumoral RI with NPI.

Pearson Correlation Coefficient	p-value
0.965	< 0.01

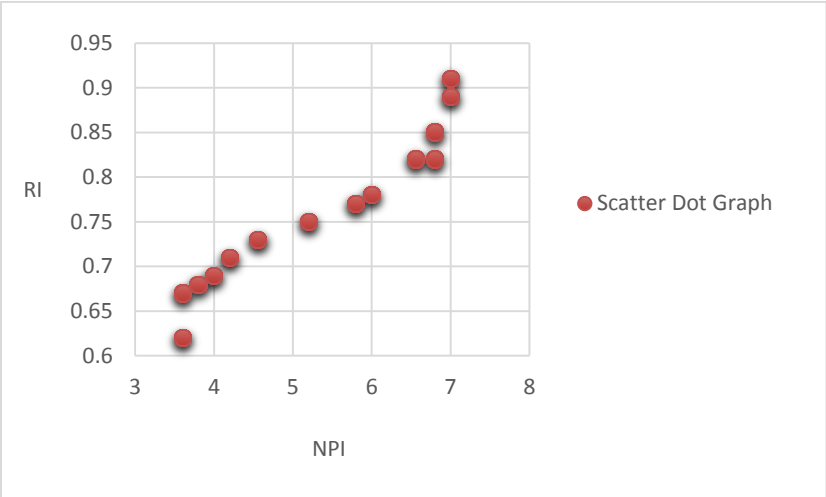

Chart 6: Scatter Dot Graph showing Correlation of intratumoral RI & NPI.

The regression analysis with scatter-dot graph shows a positive linear relationship between RI and NPI values with the p-value being < 0.01. Therefore, the correlation between the two is statistically significant.

Correlation of RI in peripheral normal breast tissue with NPI:

Table 10: Correlation of peripheral RI with NPI.

Pearson Correlation Coefficient	p-value
0.063	0.743

Therefore, the above table shows that there is no statistically significant correlation between the RI in the peripheral breast tissue and NPI.

Correlation of intratumoral RI with respect to RI of peripheral normal breast tissue:

Table 11: Correlation of intratumoral RI with peripheral RI.

Pearson Correlation Coefficient	p-value
0.000	1.000

Thus, there is no statistically significant correlation between RI of tumor and that of peripheral normal breast tissue.

From these correlation tests, it is obvious that RI in normal breast tissue does not vary significantly with invasiveness of tumor. The blood flow in such normal vessels is more or less continuous with less resistance. But in the tumor mass, neovascularization occurs with abnormal pattern of blood vessels. These vessels exhibit resistance to flow. As the invasiveness of the breast tumor increases, the resistance to flow in such abnormal vessels also increases i.e. the more is the invasiveness, the more resistant the vessel is. This is evident from the high values of RI within the tumor in cases of more invasive high grade tumors.

Therefore, there is a strong positive correlation between RI within the tumor and NPI (p-value < 0.01).

Correlation of RI with other parametric clinicopathological parameters:

Table 12: Correlation of RI with Age & Size of tumor.

Parameters	Pearson Correlation Coefficient	p-value
Age	-0.264	0.159
Size	-0.033	0.864

Correlation between these parametric variables was tested by using Pearson correlation. The Pearson correlation coefficient and p-value was calculated. The above table shows that RI does not correlate significantly with either age of the patient or size of the tumor.

Correlation of RI with other non-parametric clinicopathological parameters:

Table 13: Correlation of RI with Stage, ER, PR, HER-2/neu, grade & LN Score.

Parameters	Spearman's Rho	p-value
Stage	0.665	< 0.01
ER	-0.244	0.193
PR	-0.035	0.855
HER-2/neu	-0.248	0.187
Grade	0.794	< 0.01
L.N. Score	0.789	< 0.01

Correlation between these non-parametric variables was tested by Spearman rank correlation. The Spearman rho and p-value were calculated. Therefore, from the above table it is evident that RI correlates well with clinical stage, histological grade and lymph node score (p-value < 0.01) but does not correlate significantly with the ER status, PR status and HER-2/neu status.

DISCUSSION:

In this study, 30 female patients suffering from breast cancer and fulfilling the selection criteria of this study, were examined. The mean age of the study population was 48.47 years ± 10.543 (S.D.). The range was from 32 years to 65 years. Maximum no. of cases i.e. 18 cases (60%) were in the age group of ≥ 50 years. Among rest of the 12 cases (40%), majority i.e. 8 cases (26.7%) were aged between 35 years to 49 years whereas only 4 (13.3%) were < 35 years old. It is quite alarming that the lack of awareness and early detection programs contribute to advanced presentation of the disease.

The mean size of the breast tumor was 4.52 cm ± 1.126 (S.D.). The range was from 3 to 6 cm. The maximum no. of cases i.e. 24 cases (80%) presented with a tumor size in the range > 2 cm but ≤ 5 cm. Remaining 6 cases (20%) presented with a tumor > 5 cm. None of the patients presented with a small lump ≤ 2 cm. This again shows lack of adequate awareness and motivation among females. They often neglect small breast masses and turn up only in later stages.

All the cases were clinically staged. 2 cases were diagnosed as stage IA (6.7%), 12 cases as stage IIB (40%), 6 cases as stage IIIA (20%) and 10 cases as stage IIIB (33.3%) whereas none of the cases were in stage IB, IIA, IIIC and IV.

RI was calculated by Color Doppler ultrasonography of the breast tumor pre-operatively to detect abnormal blood flow pattern. The lowest RI within the tumor mass as well as the RI of the peripheral breast tissue (assumed to be normal) was noted. The mean intratumoral RI was 0.7520 ± 0.09309 (S.D.). The range was from 0.59 to 0.91. The standard error of mean was 0.01699 and the variance was 0.009. The mean peripheral RI was 0.6000 ± 0.01438 (S.D.). The range was from 0.58 to 0.62. The standard error of mean was 0.00263 and the variance was 0.000.

Hormonal status was assessed. Estrogen receptor status showed that 22 patients (73.3%) were ER positive whereas 8 patients (26.7%) were ER negative. Progesterone receptor status showed that 22 patients (73.3%) were PR positive whereas 8 patients (26.7%) were PR negative. HER-2/neu proto-oncogene status showed that 14 patients (46.7%) were HER-2/neu positive whereas 16 patients (53.3%) were HER-2/neu negative.

Following surgery i.e. modified radical mastectomy (MRM) with level II axillary clearance, the resected specimen was sent for histopathological examination (HPE). All tumors were graded histologically as per Scarff-Bloom-Richardson (SBR) classification. Out of 30 patients, 12 had histological grade I tumor (40%), 6 had grade II tumor (20%) and 12 had grade III tumor (40%).

22 patients had clinically apparent axillary lymphadenopathy (73.3%) among which 12 patients showed less than 3 nodes positive for metastasis on HPE (lymph node score 2) whereas rest 10 showed more than 3 nodes positive on HPE (lymph node score 3). Remaining 8 patients (26.7%) had no clinical axillary lymphadenopathy and also on HPE, they were either negative for metastasis or showed reactive hyperplasia (lymph node score 1).

Nottingham Prognostic Index (NPI) was calculated from the tumor size, histological grade and lymph node score. The mean NPI was 5.208 ± 1.3990 (S.D.). The range was from 3.2 to 7. The standard error of mean 0.2554 was and the variance was 1.957.

The regression analysis of intratumoral RI with NPI using scatter-dot graph showed a linear relationship between these two variables. Correlation test was applied to these parametric variables and the Pearson correlation coefficient of intratumoral RI with NPI was calculated to be 0.965 with p-Value < 0.01. Thus, there was statistically significant correlation between intratumoral RI and NPI.

Correlation test was also applied to RI of peripheral normal breast tissue and the Pearson correlation coefficient of peripheral RI with NPI was calculated to be 0.063 with p-Value 0.741. Thus, there exists no statistically significant correlation between peripheral RI and NPI. Correlation test between intratumoral RI and RI of peripheral normal breast tissue revealed the Pearson correlation coefficient to be 0.000 with p-Value 1.000. Thus, there exists no statistically significant correlation between intratumoral RI and peripheral RI.

From these correlation tests, it is obvious that RI in normal breast tissue does not vary significantly with the occurrence or invasiveness of tumor. The blood flow in such normal vessels is more or less continuous with less resistance. But in the tumor mass, neovascularization occurs with abnormal pattern of blood vessels. These vessels exhibit resistance to flow. As the invasiveness of the breast tumor increases, the resistance to flow in such abnormal vessels also increases i.e. the more is the invasiveness, the more resistant the vessel is. This is evident from the statistically significant positive correlation between RI within the tumor and NPI.

Similarly, Pearson correlation test was applied to other parametric variables. The Pearson correlation coefficient of intratumoral RI with age was found to be -0.264 (p-Value < 0.159) which indicated that intratumoral RI did not correlate significantly with age. Also the Pearson correlation coefficient of intratumoral RI with tumor size was found to be -0.033 (p-Value < 0.864). Thus intratumoral RI did not correlate significantly with tumor size.

Other non-parametric variables were also correlated with intratumoral RI using Spearman Rank correlation. The Spearman's rho for ER, PR and HER-2/neu were calculated as -0.244 (p-Value 0.193), -0.035 (p-Value 0.855) and -0.248 (p-Value 0.187) respectively. Therefore, intratumoral RI did not correlate with hormonal status significantly.

On the other hand, Spearman's rho for clinical stage, histological grade and lymph node score were found to be 0.665 (p-Value < 0.01), 0.794 (p-Value < 0.01) and 0.789 (p-Value < 0.01) respectively. Therefore, there was statistically significant correlation between intratumoral RI and parameters like clinical stage, histological grade and lymph node score.

There exists a positive correlation between intratumoral RI and NPI. The higher the NPI score, the higher is the value of RI, indicating that neovascularization occurs in breast cancer with increased flow resistance as per the degree of invasiveness. Also intratumoral RI correlates well with clinical stage, histological grade and lymph node score. Hence, Color Doppler ultrasonography (using intratumoral RI as the measuring index) can be considered as a potential good prognostic factor to determine the degree of invasiveness in breast carcinoma, although further investigation is necessary.

CONCLUSION:

Resistance Index (RI) within the breast tumor is found to correlate well with the Nottingham Prognostic Index (NPI) in breast cancer. The higher the NPI score, the higher was the RI value in breast cancer patients. Resistance Index (RI) of peripheral normal breast tissue does not correlate with NPI. This proves that blood flow in normal tissue is more or less continuous and does not vary significantly with invasiveness of tumor. Also intratumoral RI and peripheral RI does not have any significant correlation between them. Thus it is concluded that blood flow in normal breast tissue does not change significantly with the occurrence or invasiveness of the tumor.

Patient's age has no statistically significant relation with intratumoral RI. Size of the tumor also does not correlate with intratumoral RI significantly. Hormonal status i.e. ER, PR and HER-2/neu do not show any statistically significant correlation with intratumoral RI. Clinical stage of breast cancer, on the other hand, correlates quite well with intratumoral RI. Intratumoral RI shows a positive correlation with histological grade of tumor. Intratumoral RI also correlates significantly with lymph node score.

Therefore, Color Doppler ultrasonography with RI as the measuring index can be considered to be a good prognostic marker pre-operatively in determining the degree of malignancy, prognosis as well as the need for neoadjuvant chemotherapy in breast carcinoma and hence, in due course of time, can be expected to be a better non-invasive option than the existing conventional methods which are either costly or invasive or both.

REFERENCES:

1. Schwartz's Principles of Surgery, Ninth Edition
2. Sabiston Textbook of Surgery, 19/e (Vol. I)
3. Bailey & Love's Short Practice of Surgery, 25th Edition
4. Grainger & Allison's Diagnostic Radiology- A Textbook of Medical Imaging, 5th edition (vol. one)
5. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ: Meeting Highlights: Updated International Expert Consensus on Primary Therapy of Early Breast Cancer. J Clin Oncol 2003, 21(17):3357-65
6. Dixon JM: Breast Cancer: Diagnosis and Management, First Edition 2000
7. Sandhu DS, Sandhu S, Karwasra RK, Marwah S. Profile of breast cancer patients at a tertiary care hospital in north India. Indian J Cancer 2010; 47:16-2
8. Osanai T, Wakita T, Gomi N, Takenaka S, Kakimoto M, Sugihara K: Correlation among Intratumoral Blood Flow in Breast Cancer, Clinicopathological Findings and Nottingham Prognostic Index:Jpn J Clin Oncol 2003;33(1)14–16
9. Kim R, Osaki A, Togi T. Current & Future Roles of Neoadjuvant Chemotherapy in Operable Breast Cancer. Clin Breast Cancer. 2005 Aug; 6(3):223-32; discussion233-4
10. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological

grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991; 19:403–10
11. Blamey RW. The design and clinical use of the Nottingham Prognostic Index in breast cancer. Breast 1996; 5:156–7
12. Zafrani B, Aubriot MH, Mouret E, De Cremoux P, De Rycke Y, Nicolas A, et al. High sensitivity and specificity of immunohistochemistry for the detection of hormone receptors in breast carcinoma: comparison with biochemical determination in a prospective study of 793 cases. Histopathology 2000; 37:536–45
13. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis – correlation in invasive breast carcinoma. N Engl J Med 1991; 324:1–8
14. Cosgrove DO, Bamber JC, Davey JB, McKinna JA, Sinnett HD: Color Doppler signals from breast tumors. Radiology 176: 175-180, 1990
15. Wells PNT, Halliwell M, Skidmore R, Webb AJ, Woodcock JP: Tumor detection by ultrasonic Doppler blood-flow signals. Ultrasonics 15: 231-232, 1977
16. Burns PN, Halliwell M, Wells PNT: Ultrasonic Doppler studies of the breast. Ultrasound Med Biol 8: 127-143, 1982
17. Makes D: Breast Color Doppler ultrasound. Biomed Imaging Interv J 2005; 1(1):e6- 16
18. Lee SW, Choi HY, Baek SY, Lim SM: Role of color and power doppler imaging in differentiating between malignant and benign solid breast masses. J Clin Ultrasound 2002; 30 (8):459-64
19. Chao TC, Luo YF, Chen SC, Chen MF: Color doppler ultrasound in breast carcinomas: Relationship with hormone receptors, dna ploidy, s-phase fraction, and histopathology. Ultrasound Med Biol 2001; 27(3):351-55
20. Chao TC, Lu YF, Chen SC, Chen MF: Color Doppler ultrasound in benign and malignant breast tumors. Breast Cancer Research and Treatment 1999; 57(2):193-99
21. Choi HY, Kim HY, Baek SY, Kang BC, Lee SW. Significance of resistive index in color Doppler ultrasonogram: differentiation between benign and malignant breast masses. Clin Imaging 1999; 23:284–8
22. Hollerweger A, Rettenbacher T, Macheiner P, Gritzmann N: New signs of breastcancer: High resistance flow and variations in resistive indices evaluation by color Doppler sonography. Ultrasound Med Biol 1997; 23(6):851-56
23. Madjar H, Sauerbrei W, Prömpeler HJ, Wolfartha R, Gufler H: Color Doppler and Duplex Flow Analysis for Classification of Breast Lesions. Gynecologic Oncol 1997; 64(3):392–403
24. Youssefzadeh S, Eibenberger K, Helbich T, Jakesz R, Wolf G: Use of resistance index for the diagnosis of breast tumors. Clin Radiol 1996; 51(6):418–20
25. Peters-Engl C, Medl M, Leodolter S: The use of Color-coded and spectral Doppler ultrasound in the differentiation of benign and malignant breast lesions. Br J Cancer. 1995 January; 71(1): 137–39
26. Holcombe C, Pugh N, Lyons K, Douglas-Jones A, Mansel RE, Horgan K: Blood flow in breast cancer and fibroadenoma estimated by Color Doppler ultrasonography. Br J Surg 1995; 82(6):787–88
27. Folkman J: Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971; 285(21):1182–86
28. Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Research & Treatment 1992; 22(3):207-19
29. Mehta TS, Raza S. Power Doppler sonography of breast cancer: does vascularity correlate with node status or lymphatic vascular invasion? AJR August 1999;173(2):303-307
30. Schroeder RJ, Bostanjoglo M, Rademaker J, Maeurer J, Felix R. Role of power Doppler techniques and ultrasound contrast enhancement in the differential diagnosis of focal breast lesions: European Radiol January 2003;13(1):68-79
31. Milz P, Lienemann A, Kessler M, Reiser M. Evaluation of breast lesions by power Doppler sonography: European Radiology March 2001: 11(4);547-554
32. Yang WT, Metreweli C, Lam PKW, Chang J. Benign and Malignant Breast Masses and Axillary Nodes: Evaluation with Echo-enhanced Color Power Doppler US: September 2001 Radiology:220;795-802