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Original Article

Role of Ultrasound and Doppler Indices in Assessment of Tumor Response to Neoadjuvant Chemotherapy in Breast Malignancy

Dr.Geetika P[1*],Dr.Suresh A[2],Dr.Seema U[3],Dr.Mary Varunya J[3],Dr. Sudhanva N[1]

[1]MBBS, MD, Department of Radiodiagnosis, Vydehi Institute of Medical Sciences and Research Centre
[2]Professor & HOD, Department of Radiodiagnosis, Vydehi Institute of Medical Sciences and Research Centre
[3]Assistant professor, Department of Radiodiagnosis, Vydehi Institute of Medical Sciences and Research Centre

ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) is frequently employed in the treatment of early and locally advanced breast carcinomas. Evaluating the response of the tumor to such treatment is crucial for deciding subsequent therapeutic steps. Ultrasound and Doppler indices present as a non-invasive and cost-effective approach for this assessment. This study aims to elucidate the role of ultrasound and color doppler indices in assessing the response of breast malignancies to NAC.

Methods: Patients diagnosed with early breast carcinoma and locally advanced breast carcinoma underwent ultrasound and Color Doppler imaging to characterize the lesions. The parameters assessed included tumor size, echogenicity, tumor margins, number of flow signals, resistivity index, pulsatility index, and lymph node size. These assessments were repeated post-NAC and then compared with histopathology findings post-surgery.

Results: At diagnosis, the lesions were predominantly hypoechoic or heteroechoic with irregular margins. The mean tumor size at diagnosis was 17.05 square centimeters. Post-chemotherapy, the mean lesion size reduced to 5.92 square centimeters. There was a notable reduction in the number of flow signals, peak systolic velocity (PSV), resistivity index (RI), and pulsatility index (PI) post-NAC, especially in patients who responded well to the treatment. Using histopathology as the gold standard, ultrasound's sensitivity in gauging tumor response to NAC was 86%, while its specificity was 71%.

Conclusion: Ultrasonography, being a non-invasive, cost-effective modality without radiation exposure, proves to be a reliable tool for assessing breast carcinoma response to NAC. Such assessment is pivotal in strategizing further therapeutic plans.

Key Words: *Breast Carcinoma; Neoadjuvant chemotherapy; Ultrasonography; Doppler Color.*

***Corresponding Author**
Dr. Geetika P
MBBS, MD,Department of Radiodiagnosis, Vydehi Institute of Medical Sciences and Research Centre

INTRODUCTION

In women, breast malignancies are the most common malignancies and account for about 1/3rd of all malignancies [1]. Patients can present with palpable breast mass, nipple discharge etc., or the mass may be incidentally diagnosed. Ultrasound, Color Doppler, mammography and MRI are non-invasive methods for assessing breast lesions. Ultrasound and Color Doppler can be used to assess the size, margin, echogenicity, vascularity, resistivity index, pulsatility index etc., of these lesions and characterize them as benign and malignant [2]. Breast carcinoma is staged based on tumor size, lymph node involvement and metastasis [1]. Locally advanced breast cancer includes lesions that have spread to adjacent areas, these are prone to distant metastasis. Response to treatment decreases with more spread; hence early detection is needed.

Neoadjuvant chemotherapy assists in reducing the lesion's size to make it more operable and enable conservative surgery [2]. The surgical treatment and kind of postoperative chemotherapy are influenced by the patient's response to neoadjuvant chemotherapy.

If the tumor responds completely to neoadjuvant chemotherapy, the patient is more likely to remain disease-free and live longer. The absence of any detectable tumor remains the most significant predictor of a positive outcome [3]. Having

no visible tumor mass or having a fibrotic mass consisting entirely of destroyed tumor cells is indicative of a favourable response to therapy. Literature suggests that 75% of patients respond partially to neoadjuvant chemotherapy and 10% respond completely [4].

The efficacy of neoadjuvant chemotherapy for the treatment of locally advanced breast cancer cannot be reliably assessed using physical examination alone. Since a palpable fibrotic and necrotic mass might be misinterpreted as a residual tumor mass lesion, the accuracy of physical examination is low. Occasionally, events like hemorrhage and oedema resolve, causing the apparent clinical improvement.

Several imaging modalities like ultrasound, mammogram, MRI, elastography can be utilized for evaluating the tumor as well as tumoral response to neoadjuvant chemotherapy and to appreciate evolution of tumoral volume. Modalities can also be considered based on functional analysis (uptake of contrast media, richness of neo-vascularization) or the detection of a physio pathological tumoral activity (scintigraphy, PET scan). It is essential to assess the reliability and relevance, advantages and limitations of these imaging modalities before subjecting the patient to the study.

Ultrasound and Color Doppler can characterize the lesions pre and post-chemotherapy. This study was taken up as there are no recent Indian studies evaluating the role of ultrasound and Color Doppler in assessing tumor response to chemotherapy and also due to the contradictory results obtained in the previous studies. The goal of this research was to find out how useful ultrasonography and Color Doppler are for monitoring the effectiveness of neoadjuvant chemotherapy to treat breast cancer so that non-invasive, cost-effective method, with no radiation exposure like ultrasound and Color Doppler, can be used to assess tumor response.

OBJECTIVES OF THE STUDY

1. To determine the role of ultrasound and Color Doppler in assessment of tumor response to neoadjuvant chemotherapy.
2. To compare the grey scale and Color Doppler characteristics of lesions pre- and post-chemotherapy.
3. To compare the ultrasound characteristics of the tumor with histopathology.

MATERIALS AND METHODS

STUDY DESIGN:

This study was conducted at the Department of Radio diagnosis as a Prospective observational study to determine the role of ultrasound and Color Doppler in assessment of tumor response to neoadjuvant chemotherapy.

STUDY SETTING:

The hospital based study was conducted in the Department of Radio diagnosis of Vydehi Institute of Medical Sciences and Research Centre, Bangalore.

STUDY POPULATION:

The study population comprised of patients diagnosed cases of breast malignancy (Stage II and Stage III) referred to Department of Radio diagnosis, for ultrasonography evaluation and taking neoadjuvant chemotherapy in the institute for reduction in the size of the tumor prior to surgery.

i. Inclusion criteria:

- Stage II and Stage III histologically proven breast carcinomas
- Inoperability of the tumor at presentation.
- Patients fit for chemotherapy

ii. Exclusion criteria:

- Metastatic breast cancer
- Patient lost on follow up

STUDY PERIOD:

The study was carried out from March 2021 to September 2022 after obtaining approval from IRB (Ethical and Scientific Clearance).

SAMPLE SIZE:

The sample size has been estimated using the GPower software v. 3.1.9.4 [(Franz Faul, Universität Kiel, Germany)

Analysis:

Input:	Tail(s)	=	Two
	Effect size dz	=	0.48 [8]

	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
Output:	Noncentrality parameter δ	=	2.9197260
	Critical t	=	2.0280940
	Df	=	36
	Total sample size	=	37
	Actual power	=	0.8108628

Considering the effect size to be measured (dz) at 48% [Based on the results from previous literature by Seema Singh, et al, [24]], power of the study at 80% and the alpha error at 5%, the sample size needed is 37. The total sample needed for the present study will be 37 patients.

METHOD OF EVALUATION:

- Patients diagnosed with early breast carcinoma and locally advanced breast carcinoma (Stage II and stage III) underwent ultrasound and Color Doppler and the lesion was characterized.
- Patient's consent was taken before the scan. Philips Affinity 50G machine, linear transducer 5 – 12MHz was used.
- The parameters that were assessed during the ultrasound scan were tumor size, echogenicity, margin, no of flow signals, peak systolic velocity, resistivity index, pulsatality index and lymph node size.
- The patient then underwent treatment with neoadjuvant chemotherapy. The patient was reassessed post chemotherapy, pre surgically.
- The post chemotherapy ultrasound findings were correlated with the histopathology report from specimen from surgery.

STATISTICAL ANALYSIS

- Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp., was used to perform statistical analysis.
- Descriptive analysis of all the explanatory and outcome parameters was done using mean and standard deviation for quantitative variables, frequency and proportions for categorical variables.
- Student Paired t Test was used to compare the mean tumor size, RI and PI. of Color Doppler, lymph node size, no of flow signals between pre chemotherapy and post chemotherapy changes in tumor lesions.
- Sensitivity and specificity were calculated comparing the post chemotherpay ultrasound with the histopathology.
- The level of significance [P-Value] was set at P<0.05.

RESULTS

The study comprised a total of 37 participants who were diagnosed with breast cancer during the study period. Before participating in the study, each of these individuals underwent a clinicopathological evaluation. By using ultrasound and Color Doppler to examine the tumor, more information was gathered. Following chemotherapy, the patients underwent ultrasonography and Color Doppler again for tumor size and vascularity. Throughout the study, the following findings were noted.

Our patients average age ranged from 27 to 63 years, with a standard deviation of 8.9 years. Their mean age was 48.1 years. Most of the participants were above 50 years of age (45.9%), whereas only 2 participants were under 30 years (5.4%).

Table2:Age distributionof patients

Age(years)	No. ofpatients	Percentage
<30	2	5.4%
31 –40	5	13.5%
41-50	13	35.1%
>50	17	45.9%
Total	37	100

Out of the 37 patients diagnosed with the breast cancer, 19 patients were found to be in tumor stage T2, 8 patients in the T3 stage and 10 in stage T4. The tumor stagedistributionatpresentation isshown inTable3.

Table3:Tumorstageat the time of diagnosis

Tumorstage	No. ofpatients	Percentage
T2N0M0	6	16.2

T2N1M0	8	21.6
T2N2M0	4	10.8
T2N3M0	1	2.7
T3N0M0	1	2.7
T3N1M0	6	16.2
T3N2M0	1	2.7
T4N0M0	1	2.7
T4N1M0	8	21.6
T4N3M0	1	2.7
Total	**37**	**100**

In the current study, 8 patients were at N0 nodal status, 22 patients were at N1, 5 patients were at N2 and 2 patients were at N3 nodal status at the time of diagnosis.

Table4:Nodalstatusatthe time of diagnosis

Nodalstatus	Numberofpatients	Percentage
N0	8	21.6
N1	22	59.46
N2	5	10.81
N3	2	5.41
Total	37	100

Table7:Tumorsizeatbaseline(ultrasound examination)

TUMORSIZE	Numberofpatients	Percentage
<5cm2	4	10.8%
5-10 cm2	7	18.9%
10-20cm2	15	40.5%
>20 cm2	11	29.7%
TOTAL	37	100%
Mean (SD)	**17.05 cm2 (9.83)**	

The estrogen and progesterone receptor status as well as Her-2/*neu* statuswere assessed from the histological sample. 16 patients (43.2%) were positive forEstrogen receptor, 10 patients (27%) were positive for progesterone receptor and 13 patients (35.8 %) showed Her-2 positivity. All three markers were positive in 3 patients, while a Triple negative pattern with all 3 markers being negative was seen in 9 patients (24.3%).

Table8:Receptorstatusinthestudygroup

RECEPTORSTATUS		Number
Estrogen Receptor	Positive	16
	Negative	21
Progesterone Receptor	Positive	10
	Negative	27
Her-2/*neu*	Positive	13
	Negative	19
	Equivocal	5

ULTRASOUND ASSESSMENT:

All the patients underwent baseline ultrasound examination, and the echogenicity, margins of the lesion and the size of the lesion (mm) were measured. The size of the lesion was measured again after the chemotherapy. The size of the lymph nodes, PSV, RI and PI values were also recorded pre and post chemotherapy. The findings of the data were given in the table below. The lesion size measured at their highest diameters showed a mean of 17.05 square centimeters before chemotherapy, and post chemotherapy, the lesion size decreased by more than 50% of its baseline value to 5.92 square centimeters. The standard deviations were high due to the fact that the lesion sizes were not distributed normally in this study, and few cases were outliers when plotted on a graph. After 8 cycles of chemotherapy, both the lesion size and lymph node size were significantly reduced, and in 13 patients (35.13%) there was a 100% reduction in the lesion size. 9 patients showed a decrease of 2-60%, and 15 patients showed a decrease of 61-99%.

The lymph nodes were also found to be decreased after chemotherapy. At baseline, they had a mean size of

3.04 square centimeters, and they are reduced by 200% to 0.89 square centimeters post chemotherapy. The lymph nodes were also decreased in size post chemotherapy, with 90-100% reduction seen in 7 patients, 27 out of 37 showed 3-89% reduction, and only one patient had the lymph node size increased by just 2%.

Table 9:Ultrasound findings pre and post chemotherapy

		Mean	SD
Lesion size	**Meanlesion size at baseline (cm^2)**	17.05	9.83
	Meanlesion sizepost chemotherapy (cm^2)	5.92	7.14
Lymph Node size	**MeanLN size at baseline (cm^2)**	3.04	2.4
	MeanLN sizepost chemotherapy (cm^2)	0.89	0.84

The echogenicity of the tumor changed in the course of the chemotherapy, appearing more hypoechoic to isoechoic in the post chemotherapy images than the initial imaging, with ill-defined margins and surrounding inflammatory changes.

At the time of diagnosis and again after last cycle, Doppler evaluation of the tumor was conducted. Due to technical factors such as Doppler angle and variation in the vessel assessed pre and post chemotherapy, there was variation in the Doppler indices values. The greater standard deviation value compared to the mean revealed the wide range of variance in the velocity index data.

Doppler measurements (No of flow signals, PSV, RI and PI) were recorded at baseline and following last chemotherapy cycle. Prior to and after chemotherapy, the peak systolic velocity was evaluated, and in our study, we found that the mean PSV at baseline was 17.9 with a standard deviation of 8.1. After treatment, the PSV decreased to a mean of 9.92(SD-7.09) in partial responders and non-responders (complete responders had no vascularity).

Table 10:Doppler findings pre and post chemotherapy

	Meanvalue (SD)atbaseline	Meanvalue (SD) afterchemotherapy
PSV (cm/sec)	17.9 (8.1)	9.92 (6.68)
RI	0.7 (0.15)	0.69 (0.12)
No of Flow signals	4.05(1.99)	1.59 (1.7)
PI	1.08 (0.71)	0.85 (0.58)

The change in the Doppler indices before and after the chemotherapy were assessed, and we have found that the PSV values decreased in most of the patients and increased in 5.4% of the patients, whereas the RI values increased in 8 patients (21.6%). The change was less pronounced in RI value than in PSV values, overall.

The Pulsatality index (PI) was also found to decrease after chemotherapy with a mean decrease of 0.23. The standard deviations were higher both pre and post chemotherapy due to the fact that when the PI was decreased, it specifically decreased more in the responders than in non-responders which were the outliers in this study.

Table11:ChangeinDopplerindicesafterchemotherapy

	PSV		RI		PI	
	N	**%**	**N**	**%**	**N**	**%**
Nochange	0	0	0	0	0	0
Increase	2	5.4%	8	21.6	5	13.5
Decrease	35	94.5%	29	78.3	32	86.4
Total	37	100	37	100	37	100

When we compared the parameters with baseline ultrasound examination and post chemotherapy assessment, we identified and classified the participants into partial, complete and non-responders based on WHO criteria (<50 % decrease in size considered as non-responders, >50% decrease in size considered as partial responders and 100% decrease in size considered as complete responders). On ultrasound assessment, we have found that there were 15 partial responders (40.5%), 13 complete responders (32.4%), and 9 participants did not respond to the chemotherapy treatment (27.03%).

Table 12: Responders on Ultrasound assessment

		Frequency	Percent
Ultrasound response	**Partial responders**	15	40.5%

	Complete Responders	13	35%
	Non responders	9	24.03%
	Total	37	100.0

In the study, a post-operative assessment of the specimen was carried out, and the relevant histopathological findings were measured including the lesion size, nodal response etc., The responders were classified using pathological response in the tumor, and as well as based on the nodal status of the patient.

54.1% of the patients were partial responders, and 18.9% were non responders in the histopathological response assessment scoring. 10 participants (27%) were complete responders, which is close to the response assessed in ultrasound.

Table 13: Responders on histopathological assessment

Histopathological Response	Frequency	Percent
Partial responders	20	54.1
Complete Responders	10	27.0
Non responders	7	18.9
Total	37	100.0

When we compared the response accuracy of ultrasound, using the pathological response as the gold standard, we understood that ultrasound was not able to identify three residual lesions and categorized them as complete responders, and categorized one histopathologically completely responsive patient as partial response. The sensitivity and specificity of the ultrasound, using HPE response as the gold standard showed high sensitivity and specificity for the prediction. This association was found to be significant statistically, with a p value of <0.01.

The specificity of the ultrasound was lower than that of sensitivity in our study. The sensitivity of the test was 86.6% (95% CI: 69.28% to 96.24%), and the specificity was 71.43%. The overall accuracy of the ultrasound in identifying the responders came to be 79.05% (95% CI: 62.54% to 90.64%).

Table 14: Comparison of Ultrasound response with HPE response

SONOGRAPHICRESPONSE	HISTOLOGICALRESPONSE			TOTAL	P value
	Partial responders	Complete Responders	Non responders		
Partial responders	13	1	1	15	<0.01
Complete Responders	3	9	1	13	
Non responders	4	0	5	9	
TOTAL	20	10	7	37	

Table 15: Test validity of Ultrasound response with HPE response as gold standard

S No	Validity Parameter	Percentage	95% Confidence Intervals
1	Sensitivity	86.6%	69.28% to 96.24%
2	Specificity	71.43%	29.04% to 96.33%
3	Positive Predictive Value (*)	75.21%	48.25% to 90.80%
4	Negative Predictive Value (*)	84.27%	65.76% to 93.73%
5	Accuracy (*)	79.05%	62.54% to 90.64%

The baseline ultrasound and Doppler characteristics were compared with the histopathological response in below table. The baseline PSV values showed a high mean value (23.85) in all the non-responders compared to the complete responders, and this association was significant (p<0.01). The baseline RI values did not show much difference between the responder groups, but the mean RI in the non-responders was still high (0.74), when compared to mean values seen in

partial and complete responders (0.71, 0.66 respectively). This association was also statistically significant with a p value of <0.01.

When we measured the flow signals distribution in the patients with HPE response, we observed that with a mean of 5.42, non-responders had high number of signals than complete responders (3.2). Partial responders showed an average of 4 signals in their pre-treatment evaluation.

The baseline measurement of the tumor size was also distributed unequally among the participants with HPE response, showing a bigger tumor (mean tumor size= 22.26 cm2) in the non-responders, and a smaller tumor (10.69 cm2) in complete responders.

Table 16: Pre-treatment Ultrasound and Doppler characteristics versus histological response.

	Partial Responder	Complete Responders	Nonresponders	pvalue
Mean baseline PSV	17.95	13.8	23.85	<0.01
MeanbaselineRI	0.714	0.66	0.74	<0.01
Mean baseline Flow signals	4	3.2	5.42	<0.01
Mean baseline lesion size (cm2)	18.39	10.69	22.26	<0.01
Mean baseline PI	1.17	0.82	1.22	<0.01

The same characteristics were repeated after the 8 cycles of chemotherapy in the patients, and the results were tabulated below. All the variables showed a change in their values. Similar to baseline values, the PSV values were higher in non-responders (Mean PSV=16.85). Partial responders showed a mean PSV value of 6.35 after treatment.

The RI values have changed post treatment, with mean of 0.56 for partial and 0.71 for non-responders. PI value also significantly changed in the responders compared to the non-responders, showing that the mean PI value (1.0) remain high in the non-responders post chemotherapy, but showed a decrease in the value in partial responders.

Similarly, the flow signals also showed a significant reduction in complete and partial responders compared to non-responders. Lesion size decreased significantly in the responders compared to the non-responders (with highest mean 14.25 still in the non-responders).

Table 17: Post chemotherapy Ultrasound and Doppler characteristics versus Histological response.

	Partial Responder	Nonresponders	pvalue
Mean PSV	6.35	16.8	<0.01
MeanRI	0.56	0.71	<0.01
MeanFlow signals	1.45	4	<0.01
Mean lesion size (cm2)	2.06	14.25	<0.01
Mean PI	0.66	1.0	<0.01

When we measured how much of the lesion has decreased in the responders (partial and complete responders) and non-responders, we observed more than 75% decrease in 30 responders, and in non-responders no one has showed a decrease more than 75%. All 7 non-responders showed either a decrease of 75% and less or an increase in the tumor size.

Table 18: Percentage decrease of lesion size in HPE response

Lesion size (Percentage decrease)	Responders	Non responders
<25%	0	3
26-75%	4	4
>75%	26	0
TOTAL	30	7

Similarly, the PSV values were also measured for the percentage decrease, and only 1 non responder showed a 99% decrease in their PSV values, compared to 17 responders showing more than 75% decrease.

Table 19: Percentage decrease of PSV in HPE response

PSV (Percentage decrease)	Responders	Non responders
<25%	3	3

26-75%	10	3
>75%	17	1
TOTAL	30	7

None of the Non-responders has shown a decrease above 25% in the RI values. Even in the responders, only 11 out of 30 showed a decrease of more than 75%, whereas 8 out of 30 showed an increase in the values post chemotherapy. Histopathology was able to distinguish the responders from non-responders based on the percentage decrease in their RI values correctly. This association was found to be statistically significant ($p<0.01$)

Table 20: Percentage decrease of RI in HPE response

RI (Percentage decrease)	Responders	Non responders
<25%	15	7
26-75%	4	0
>75%	11	0
TOTAL	30	7

In the present study age of the patient, tumor grade and nodal status at presentation didnot correlatewith histologicalresponse significantly. All of the non-responders fell in above 40 years of age, and this association although appears important, was found to be statistically not significant. The responders were also more in the 50 years age group, which concludes that age did not affect the outcome in this study.

Table 21: Association of age with the HPE response

AGE	**Partial Responder**	**Complete Responders**	**Nonresponders**	**P value**
<30 years	1	1	0	0.553
31-40 years	2	3	0	
41-50 years	7	3	3	
>50 years	10	3	4	

When we compared the tumor stage at presentation with the histological response, we observed that patients with stage IIIA and lower has responded to treatment well than those in IIIB and IIIC. This, however was not significant statistically. There were 3 non responders in those with stage IIB, and 3 in those presented with stage IIIB.

Table 22: Association of cancer stage with the HPE response

STAGING	**Partial Responder**	**Complete Responders**	**Nonresponders**	**P value**
IIA	3	2	1	0.593
IIB	5	2	3	
IIIA	8	2	0	
IIIB	4	2	3	
IIIC	1	1	0	

Finally, we compared the location of tumor and echogenicity of the tumor with the HPE response, and found this relationship also to be not significant. Tumors on the left breast responded almost equally with the tumors in right breast, with 8 out of 11 has responded in left breast, and 22 out of 26 in right breast.

Limitation of our study is that our study included small sample size of 37patients. Larger sample size may be necessary to accurately establish the role of Ultrasound and Color Doppler in assessing tumor response to neoadjuvant chemotherapy. Significant conclusion could not be obtained regarding elastography changes in pre and post neoadjuvant chemotherapy as data could be collected only for a few patients after the installation of the elastography software. In the data collected for 6 patients it was seen that the strain ratio reduced in the post chemotherapy images compared to the prechemotherapy images.

Illustrative cases

1) 55-year-old female presented with history of breast lump since 6 months. Clinical examination revealed a lump in the right breast and the patient was subjected to breast ultrasound.

Prechemotherapy images:

Figure 1A: Hypoechoic lesion with irregular margins **(⇨**with no calcifications, no satellite lesions in the right breast at 11-2 0'clock position measuring 58 x 29mm.

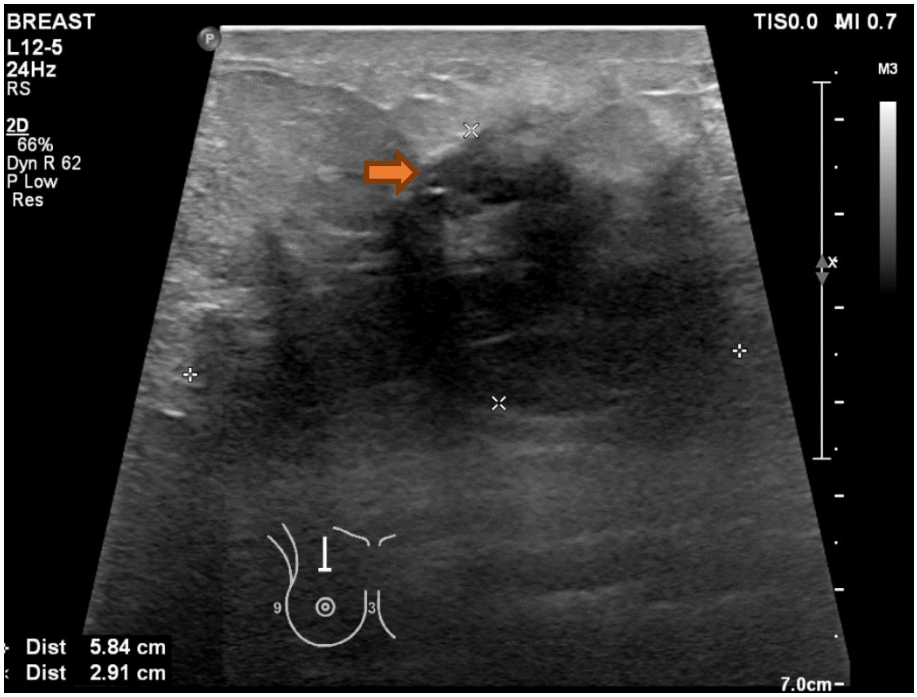
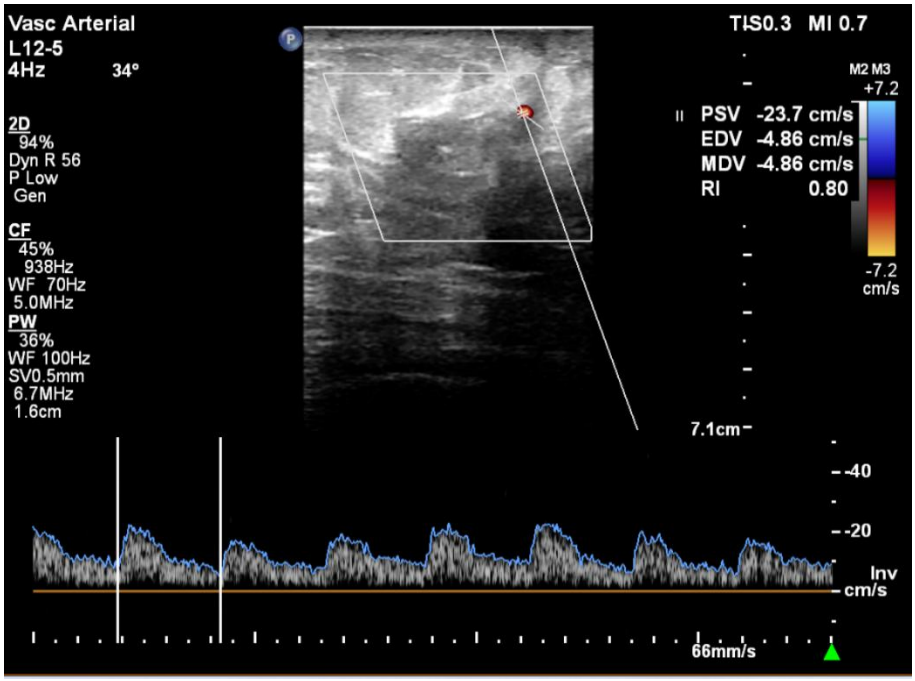


Figure 1B: On Doppler interrogation internal vascularity was noted with PSV of 23.7, RI of 0.8 and PI of 0.88.



Post chemotherapy images:

Figure 1C: The ultrasound image revealed an heteroechoic residual lesion

( ) measuring 12 x 7.5mm showing partial response.

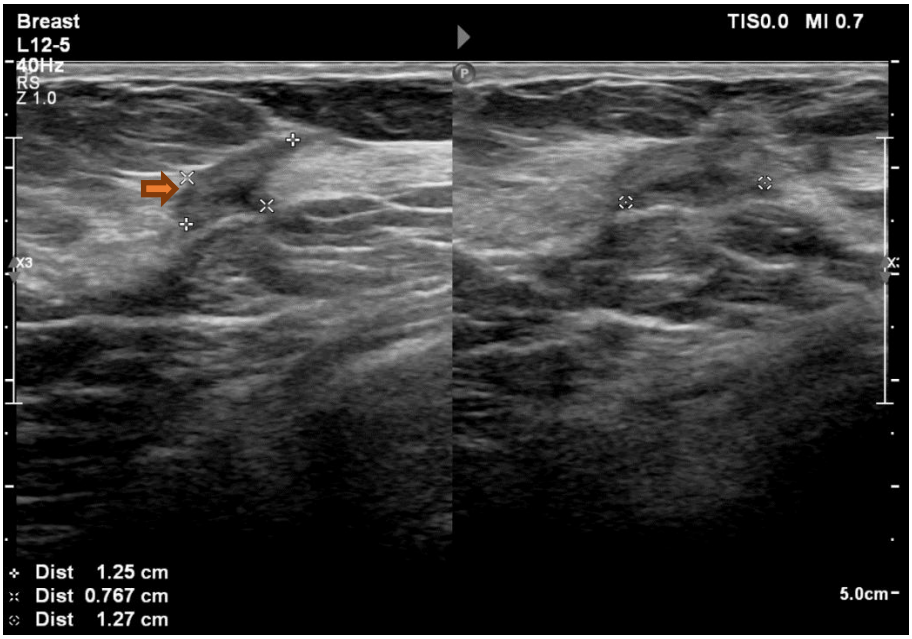
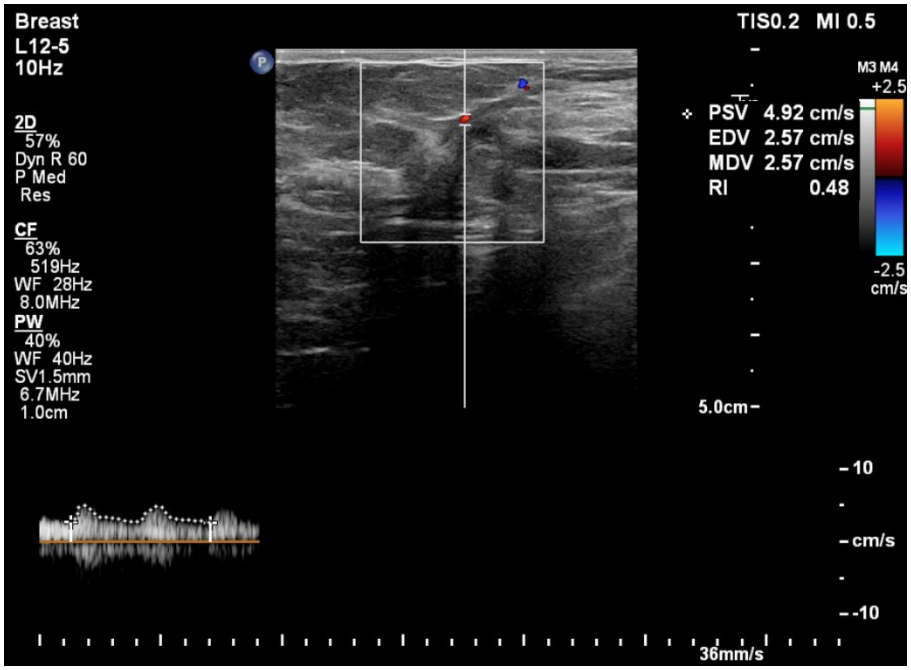


Figure 1D: On Doppler interrogation internal vascularity was noted with PSV of 4.92, RI of 0.48 and PI of 0.65.

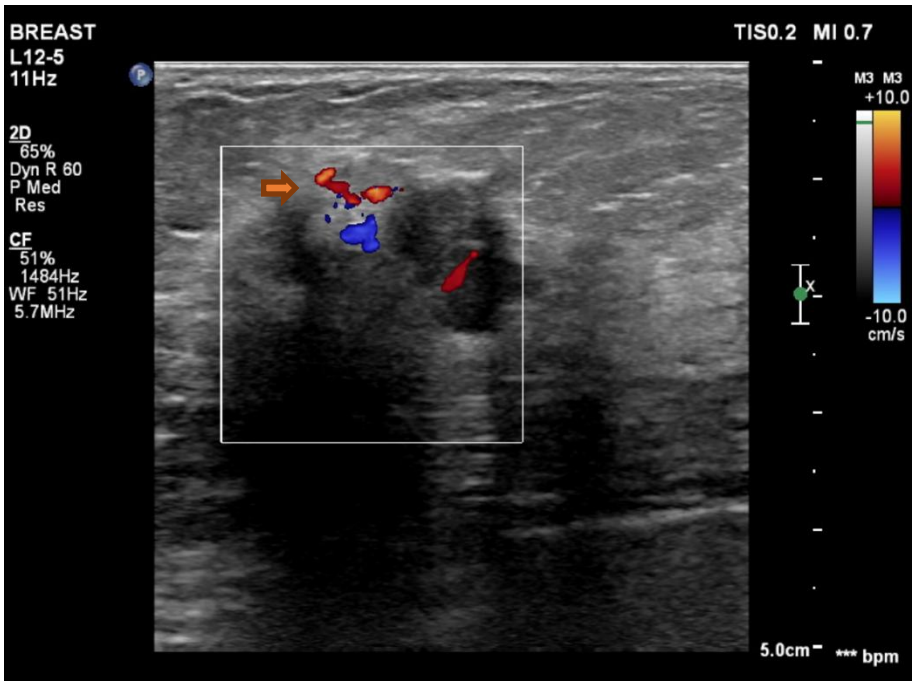


2) 43-year-old female presented with history of right breast lump since 1 month. Clinical examination revealed a lump in the right breast and the patient was subjected to breast ultrasound.

Prechemotherapy images:

Figure 2A: Hypoechoic lesion (⇨) with irregular margins, with no calcifications, no satellite lesions in theright breast at 9-10 0'clock position measuring 28 x 15mm.

Figure 2B: On Doppler interrogation internal vascularity noted with 4 flow signals ⇨



Post chemotherapy images:

Figure 2C: Residual lesion measuring 8 x 10mm (➡) showing partial response.

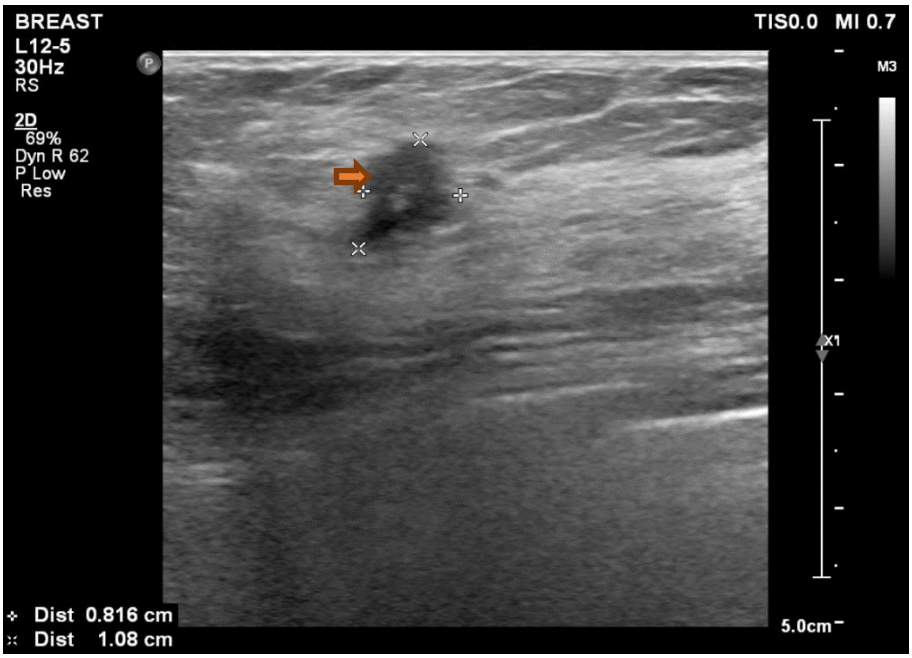
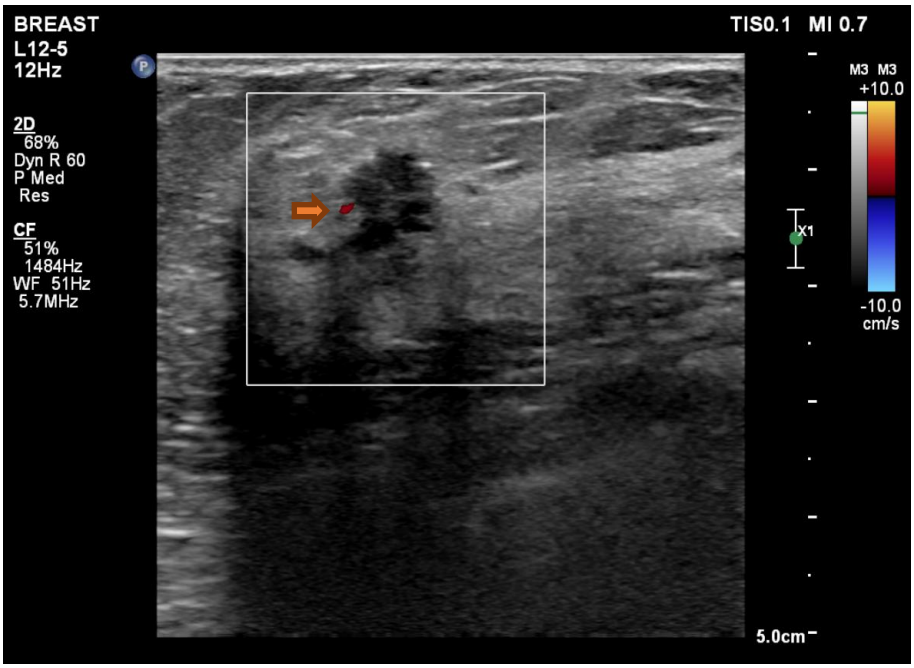


Figure 2 D: On Doppler interrogation reduced internal vascularity noted with 1 flow signal (➡)



DISCUSSION

In developing countries like India, breast cancer is one of the most prevalent cancers in women. At the time of diagnosis, majority of the patients in India (45.7%) present with locally advanced and metastatic stages [5].Neoadjuvant chemotherapy is one of the accepted courses of treatment for those with locally advanced breast cancer. Patients who have taken neoadjuvant can undergo breast conservation surgery or modified radical mastectomy based on their response to chemotherapy.

A primary tumor's clinical response to Neoadjuvant chemotherapy verifies the tumor's sensitivity to those particular medications. A different type of systemic therapy or surgical intervention may be used if no response is seen to the chemotherapy regimen. It also helps in preventing unnecessary toxicity caused by these drugs. Understanding the response of chemotherapy before proceeding to surgery is one of the most important steps in assessing prognosis of the disease.

In our study, we included 37 patients with a mean age of 48.1 years, which correlates with the fact that the most breast cancers were seen in the age group of above 45 years. [5] But there was no significant difference in the response rates ofwomenwith different age groups. Although we found that the response tends to diminish a little in those above 55 years old.

In our study 19 patients were seen in T2 tumor stage, 8 were seen in T3 stage and 10 patients were seen in T4 stage. Response to chemotherapy was poor in the T3 and T4 stages compared to those in T2 stage.

In our study, 16% of patients were in IIA, 27% in IIb, another 27% in IIIA, 24.3% in IIIIB and 5.4% in IIIC. Most of the patients were in earlier stage of breast carcinoma. This is probably due to the fact that being a tertiary care centre in urban locality, early diagnosis of the disease was carried out on most population attending hospitals. In a study done by Kunnuru et al [6], they found a significant association of tumor response to neoadjuvant chemotherapy with the cancer stage at presentation. Early carcinomas responded much better than advanced cancers, and most of the stage III tumors at presentation went to stage I or II post chemotherapy. In 32 patients of T4 stage, who underwent chemotherapy, only 13% of them stayed in the same T4 stage after the NAC. Our study also showed that since most of our participants were in early-stage breast cancers, they responded well to the chemotherapy compared to those in the late stages.

We observed 59.46% of patients with N1 nodal status, 10.81% in N2 nodal status and 5.41% in N3 nodal status at the time of diagnosis. 21.6 % of the patients did not show any nodal involvement.

The receptor status in the current study group showed 70.2% positivity for Estrogen or /progesterone receptor and 35.8 % were having Her-2/neu positivity. A triple negative pattern of all 3 markers was found in 24.3%, which was in line with the global estimates of 15-25%. Govardhan et al studied the markers in his patients, and 40% showed a positive Her-2/neu status, and more than 60% had estrogen and progesterone receptor positive. [7]

Clinical examination is routinely done is assessing breast tumor. Various radiological imaging modalities can be used to assess breast carcinoma like ultrasound, mammography, elastography, MRI etc. which help in further characterization of the lesion and also assessing the extent of the tumor. It can also help in staging of the tumor at the time of diagnosis to decide further treatment plan. In our study we used ultrasound and Color Doppler to assess the breast carcinoma at the time of diagnosis and also following the neoadjuvant chemotherapy.

In our study 26 patients had tumor on the right side and 11 patients had it on the left side. The mean size of the tumor in our study was 17.05 square centimeters in the pre chemotherapy scan at the time of diagnosis. 29.7% of the patients in our study showed a tumor more than 20 square centimeters, and only 10.9% have a tumor less than 5 square centimeters at the time of diagnosis. After taking neoadjuvant chemotherapy the tumor size significantly deceased in size in ultrasound in majority of the patients (28 patients). In our study, after 8 cycles of chemotherapy, the mean lesion size was shown to be decreased to 5.92 square centimeters. It showed a decrease by more than 50% of its baseline prechemotherapy size. In 35% of the patients there was a 100% reduction in the lesion size. This is probably due to the fact that most of our participants were in early stage of the disease with smaller tumor size and hence showed good response to chemotherapy compared to other studies. According to the sonographic measures used in the study by Lonedro et al., the tumor's mean diameter was 32.4 mm prior to treatment; 27.4 mm after two cycles of chemotherapy, and 17.3 mm after chemotherapy was finished.[8]

Post neoadjuvant chemotherapy after the patient underwent breast conservative surgery or modified radical mastectomy the post-operative histopathology was compared with the post chemotherapy ultrasound. When we calculated the sensitivity and specificity of ultrasound using pathological response as gold standard, we found that sensitivity of USG is 86%, and specificity is 71%. Annina Baumgartner et al. [14], in their retrospective study of 124 invasive breast carcinoma cases assessed the predictive power of ultrasound in accurately determining complete pathological response and it showed that sensitivity was 60.8% and specificity 78.0% for prediction of remission of

tumor by Ultrasound. Another study by Hamisa et al identified a good correlation between ultrasound response and pathological response with a Pearson correlation coefficient of 0.576. According to them, diffusion weighted MRI was the most effective method to assess response to neoadjuvant chemotherapy than ultrasound or Doppler.[9]

In our study 10 patients showed complete response on both ultrasound and histopathology. However, three patients that were considered as complete response in ultrasound showed positive for tumor cells in the histopathology. Hence at least a breast conservation surgery should be performed after the chemotherapy in cases showing complete response in ultrasound, to prevent growth from the residual tumor cells. Another two patients who were diagnosed as non-responders on ultrasound were found to be responders on histopathology. This may be due to the surrounding fibrotic mass being considered as the lesion and leading to overestimating the tumor size.

The relationship between tumor size and chemotherapy response was significant, with tumors smaller than 5 square centimeters showed better response than those that are bigger than 20 square centimeters. This is similar to Gajdos etalwho also reportedbetterresponseratesinsmallertumors.[10]

The echogenicity of the tumor was found to be hypoechoic or heteroechoic in prechemotherapy ultrasound with few (13 patients) showing calcifications at the time of diagnosis. In the post chemotherapy ultrasound, most of the lesions showed further decrease in echogenicity appearing more hypoechoic or cystic. The margins of most tumors were irregular in the pre chemotherapy ultrasound. After undergoing chemotherapy, the margins appeared ill-defined with significant inflammatory changes in the surrounding breast tissue compared to the prechemotherapy ultrasound images.

We assessed the baseline values of PSV, RI, PI and number of flow signals in the patients in our study using Doppler, and these were repeated after chemotherapy. We have observed that the PSV values increased in 5.4% of the patients, whereas the RI values increased in 8 patients (21.6%). When compared to the complete responders, all of the non-responders' baseline PSV values had a higher mean value (23.85), and this association was statistically significant ($p<0.01$). When compared to mean values seen in partial and complete responders, the baseline RI values did not reveal much variation between the responder groups, although the mean RI in non-responders remained high with a value of 0.74. The Pulsatality index (PI) was also found to decrease after chemotherapy with a mean decrease of 0.23. The standard deviations for PI were higher both pre and post chemotherapy due to the fact that there were outliers. When the PI was decreased, it decreased more in the responders than in non-responders.

A study by Singh G et al [11] showed that there was a decrease in mean PSV, PI and RI in responders after chemotherapy when compared to the prechemotherapy mean PSV, PI and RI. In the non-responders PSV, PI and RI increased in post chemotherapy. Another study by Kumar A et al [12], discovered that the Mean (SD) of the RI value was 0.756 (0.246) at the time of presentation, and that 4 out of 50 patients (8%) showed an increase in RI after treatment.

In our study the number of flow signals decreased after the patient underwent chemotherapy indicating the decrease in the internal vascularity of the tumor hence indicating a response to treatment. It decreased more in the responders than the non-responders.

The lymph nodes were also found to be decreased after chemotherapy. At baseline, they had a mean size of 3.04 square centimeters, and they are reduced to 0.89 square centimeters post chemotherapy. 90-100% reduction was seen in 7 patients, 27 out of 37 showed 3-89% reduction, and only one patient had the lymph node size increased by just 2%.

The overall response rate in this study as observed by ultrasound was 75.7%. The pathological response rate we found in our study was 81.1%, which is concordant with manystudies which have reported a response of 85 – 90% to chemotherapy. Seven patients did not respond to chemotherapy while the reportedrate of non-responders using ultrasound examination was 24.3%.

A study done by Matthes et al [13], showed that in most cases MRI demonstrated a better correlation than the other imaging exams in the definition of tumor measurement after neoadjuvant chemotherapy. Its drawback is that its expensive and is not available in the rural centers. Though MRI is a more sensitive modality for assessing breast carcinoma cases undergoing neoadjuvant chemotherapy, ultrasound and Color Doppler being non-invasive, cost-effective, easily available method with no radiation exposure, with high sensitivity and specificity can be used to assess breast carcinoma cases undergoing neoadjuvant chemotherapy.

The assessment of response to chemotherapy is important as it helps in the further management of the patient. Patients not responding to chemotherapy can discontinue the course to avoid the toxic effects of the medications and patients responding well can undergo a breast conservative surgery instead of a more extensive modified radical mastectomy if the residual lesion is small.

CONCLUSION

Breast carcinoma is one of the most common carcinomas in India. Neoadjuvant chemotherapy is one of the accepted courses of treatment for those with locally advanced breast cancer. Patients who responded well to neoadjuvant can undergo breast conservation surgery or modified radical mastectomy based on their response to chemotherapy. Hence assessment of response to chemotherapy is important in planning the surgery. Various radiological investigations can be used to assess the response. In our prospective study including 37 patients we determined the role of ultrasound and Color Doppler in assessing the response and we found that ultrasound has a good sensitivity and specificity in assessing the response of breast carcinoma to chemotherapy. The tumor size, lymph node size, no of flow signals, peak systolic velocity, resistivity index and pulsatality index decreased after neoadjuvant chemotherapy compared to the baseline values (at the time of diagnosis) in the patients responding to chemotherapy. It can hence be concluded that ultrasound which is a non-invasive, cost-effective, easily available method with no radiation exposure can be used to assess breast carcinoma cases undergoing neoadjuvant chemotherapy

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REFERENCES

1. Kasper, Fauci, Hauser, Longo, Jamson, Loscalzo(2018). Harrison's principles of Internal Medicine. 20th edition. United States of America:McGraw Hill publishers;p.555,558.
2. Dobruch-Sobczak K, Piotrzkowska-Wróblewska H, Klimonda Z, Roszkowska-Purska K, LitniewskiJ(2019). Ultrasound echogenicity reveals the response of breast cancer to chemotherapy. Clin Imaging;55:41-46.
3. Feldman LD, Hortobagyi GN, Budzar AU, Ames FC, FlumenscheinGR(1986). Pathologic assessment of response to induction chemotherapy in breast cancer. Breast Cancer Res Treat; 46: 2578–81.
4. Moskovic EC, Mansi JL, King DM, Murch CR, Smith IE(1993). Mammography in the assessment of response to medical treatment of large primary breast cancer. Clin Radiol; 47:339–44.
5. Eisenhauer EA, Bogaerts J, Therasse P, Sargent D, Schwartz LH et al(2009). New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer; 45: 228–247.
6. Kunnuru SKR, Thiyagarajan M, Martin Daniel J, Singh K B(2020). A study on clinical and pathological responses to neoadjuvant chemotherapy in breast carcinoma. Breast Cancer (Dove Med Press);12:259–66.
7. H. B. DG, Thimmaiah DN, I DK, Kashyap DL, Goyal DS, Pradhan DS, et al(2016). Correlation of Clinical Examination, Mammography and Color Doppler Ultrasonography with Histopathological Findings in Patients of Carcinoma Breast Undergoing Neo-adjuvant Chemotherapy. International Journal of Medical Research and Review;4(5):810–9.
8. Londero V, Bazzocchi M, Del Frate C(2004). Locally advanced breast cancer: comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. EurRadiol;14(8):1371–9.
9. Hamisa M, Dabess N, Yosef R, Zakeria F, Hammed Q(2015). Role of breast ultrasound, mammography, magnetic resonance imaging and diffusion weighted imaging in predicting pathologic response of breast cancer after neoadjuvant chemotherapy. Egypt J RadiolNucl Med;46(1):245–57.
10. Gajdos C, Estabrook A, Tartter PI et al(2002). Relationship of clinical and pathologic response to neoadjuvant chemotherapy and outcome of locally advanced breast cancer. Journal of Surgical Oncology; 80(1):4-11.
11. Singh G, Kumar P, Parshad R, Seith A, Thulkar S, Hosten N(2010). Role of color Doppler indices in predicting disease-free survival of breast cancer patients during neoadjuvant chemotherapy. European journal of radiology;75(2):e158-62.
12. Singh S, Pradhan S, Shukla RC, Ansari MA, Kumar A(2005). Color Doppler ultrasound as an objective assessment tool for chemotherapeutic response in advanced breast cancer. Breast Cancer;12(1):45-51.
13. MatthesAGZ(2010). Clinical,radiologic and pathologic evaluation of locally advanced breast cancer in patients submitted to neoadjuvant chemotherapy. PhD Thesis - Botu- catu Medical School.
14. Baumgartner A, Tausch C, Hosch S, Papassotiropoulos B, Varga Z, Rageth C, BaegeA(2018). Ultrasound-based prediction of pathologic response to neoadjuvant chemotherapy in breast cancer patients. Breast;39:19-23.