Global Surgery

Research Article ISSN: 2396-7307

Role of breast ultrasound in evaluating the response of locally advanced breast cancer to neoadjuvant anthracycline chemotherapy in Ibadan

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Abstract

Introduction: Neo-adjuvant chemotherapy (NAC) is increasingly used in the treatment of patients with large and locally advanced breast cancer (LABC). It aims at downsizing the primary tumor thereby minimizing micro-metastatic disease. There exists variable response following neo-adjuvant chemotherapy and the objective of this study was to determine the potential role of breast ultrasound in monitoring the clinical response of LABC to NAC.

Methods: One hundred and twenty (120) consecutive patients with LABC scheduled to have six cycles of anthracycline-based neo-adjuvant chemotherapy were recruited for the study at the Surgical Oncology Unit of the University College Hospital, Ibadan. Eligible patients had a pre-chemotherapeutic breast ultrasound (US). Follow up breast US was performed 3 weeks after completion of each cycle of chemotherapy. Ethical approval was obtained from the University of Ibadan/ University College Hospital Ethics Committee and data analyzed using SPSS Software version17.0, Chicago, Illinois.

Result: The mean age of the women studied was 44.17 ± 9.07 years with peak age group in the 5th decade. Breast ultrasound detected more multifocal disease in 42 (35%) patients compared to 2 (1.7%) patients on clinical breast examination (CBE), so also detected nodal disease in 5% more patients than CBE. There was 91.6% agreement between CBE and breast ultrasound in nodal staging, p= 0.001 compared to 60% in tumor staging, p = 0.52. A good clinical response was found in 106 (88.3%) patients exposed to neo- adjuvant chemotherapy. No predictor of tumor response to neo-adjuvant chemotherapy was found in this study.

Conclusion: Breast ultrasound is more appropriate than CBE in the pre- or post-chemotherapy assessment of tumor size and nodal staging in patients with breast cancers. In this study, breast ultrasound agreed more with clinical breast examination in nodal staging than in tumor staging and it was vital in the detection of multifocal breast cancers. Although it is quite difficult to predict patients that would respond well to NAC, anthracycline- based chemotherapy remains effective in patients from low income countries.

Background

Neoadjuvant chemotherapy (NAC) has become a veritable tool for down-staging of locally advanced breast cancer (LABC) [1,2], immediate treatment of micro metastases [3,4] and direct assessment of drug efficacy [5]. It has become as pivotal as adjuvant chemotherapy (AC) in the management of locally advanced breast carcinoma. In the sub Saharan African setting the typical patient often presents with an advanced tumor [6,7] that often precludes immediate surgical extirpation. Approximately 50% of breast cancer patients seen in our oncology practice require NAC to downstage and render the tumor amenable to loco-regional surgical treatment [7]. Many studies have demonstrated that the degree of tumor response and the extent of residual disease after adjuvant chemotherapy are predictors of relapse and survival [8-10].

The response of the primary tumor or regional nodes has been monitored clinically by palpation and found unreliable as it tends to overestimate the number of complete remission while underestimating the number of non-responders [5]. While radiological monitoring, be it mammogram, ultrasound, magnetic resonant imaging (contrast enhanced) or radio-nuclide imaging, has been used by various authors with published results [11-14], the gold standard modalities (breast magnetic resonance imaging and pathologic response) for monitoring response to NAC [5] are however not always possible in the sub-Sahara African setting for reasons of affordability, limited technology penetration and large specialist to patient ratio.

However, breast ultrasonography has become an accepted adjunct to mammography for the evaluation of the breast after treatment for cancer in most countries in sub-Saharan Africa because it is readily available, affordable, non- invasive and is employed as an alternative diagnostic tool in assessing breast pathologies.

We set out to determine the objective response rate of LABC to NAC using breast ultrasound scan in characterizing and evaluating these responses. We also sought for the clinico-pathologic factors that might predict response to NAC. The findings from this work are the thrust of this paper.

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Received: May 29, 2018; **Accepted:** July 20, 2018; **Published:** July 23, 2018

Materials and methods

This was a prospective cross-sectional study of ultrasound assessment of response of women with LABC to neo-adjuvant chemotherapy. Institutional ethical approval was obtained prior to the commencement of the study. All consecutive patients presenting with locally advanced breast carcinoma (Stage IIb- Stage IIIC) at the surgical out-patients clinic of the University College Hospital, Ibadan between January and December 2013 were recruited. Tissue diagnosis was confirmed either with a fine needle aspiration cytology (FNAC) or core needle biopsy. Individuals less than 18 years or above 70 years, those with metastatic breast cancer or early stage breast cancer (Stage I–IIa), male breast cancer patients and those who declined participation were excluded from the study. This was a prospective cross-sectional study and a total of 120 consecutively diagnosed women with LABC were recruited. Pre-treatment evaluation included a clinical breast examination (CBE), core biopsy/ fine needle aspiration cytology, radiologic investigations (chest x-ray, abdomino-pelvic ultrasound scan, bone radionuclide scan) along with breast ultrasound scan. Breast ultrasonography was done using a Logiq PS ultrasound machine with 7.5-10 MHz Linear probe to fully characterize the breast lump and assess skin thickening, architectural distortion and nipple retraction. The characteristics of the lump assessed with ultrasonography were pattern, location, size, shape, margins, echotexture, orientation, vascularity and attenuation. The number, size and morphology of the ipsilateral axillary lymphadenopathy was also assessed. Further work-up before commencing treatment included cardiac assessment (echocardiogram and electrocardiography) to ascertain fitness for anthracycline based chemotherapy and routine complete blood count. Neo-adjuvant treatment entailed anthracycline based chemotherapy (Epirubicin@100 mg/m^2 and Cyclophosphamide@1000 mg/m^2) at 3 weeks intervals. Pre-chemotherapy medications included dexamethasone, ondansetron and chlorpheniramine given intravenously at least thirty minutes before infusing the chemotherapeutic agents. The protocol of the study for each patient consisted of pre-chemotherapy breast ultrasound scan, chemotherapy infusion, and repeat breast ultrasound scan before subsequent chemotherapy administrations.

In the ultrasound suit, the patient was placed in supine position with the ipsilateral arm positioned above the head. The breast was scanned in both longitudinal and transverse planes with radial and anti-radial planes used to illustrate the breast anatomy better. Lump size measurement was taken in 3 dimensions (breadth, width and length) with a product of the maximum two used in monitoring and assessing response. The above measurements were taken thrice, and the average recorded to minimize intra-observer variation. Tumor response was correlated with the standard International Union against Cancer (UICC) criteria [15]. Other data collected from the patient's records included demographic information, clinico-pathologic findings and clinical response.

Statistical analysis was done using SPSS version 18.0 for windows vista. Descriptive statistics included frequency tables, means, standard deviations, graphs and diagrams. Parametric paired comparisons of mean values were performed using the paired t-test. Measure of agreement between ultrasound and clinical breast examination was evaluated using Cohens Kappa method. *P* value of <0.05 was considered significant (95% confidence interval).

Results

A total of 120 consecutive patients with LABC receiving anthracycline-based chemotherapy was recruited. The mean age was 44.17 ± 9.07 (range 25–70 years). Two-fifths (40%) were in the 40–49 age group. The mean weight and height was 71.73 ± 15.9 kg and 1.64 ± 0.1 m respectively. About a quarter (26.7%) were obese with BMI ≥ 30. A fifth of the pathologic diagnosis was achieved by cytology while four-fifths were by core biopsy.

Table 1 shows the demographic and clinico-pathologic characteristics while table 2 shows the ultrasound scan findings of the malignant breast lesions.

The average pre-chemotherapy breast lump diameter on clinical examination was 11.43 ± 4.42cm. This figure reduced to 6.26 ± 2.42cm on ultrasound scan (USS) (Table 3). The widest diameter on clinical breast examination (CBE) ranged from 4.8-20 cm against 2.5-11.9 cm from USS (p value <0.001). The axillary nodal state was missed in 6 patients (5%) on CBE. There was concordance with the USS findings in the remaining 114 (95%) patients. The ultrasound scan was able to delineate multiple discrete lesions in the breast in 42 (35%) patients as against 2 (1.7%) patients on CBE when measured before commencement of neo-adjuvant chemotherapy. The mean post chemotherapy tumor diameter was 2.82 ± 1.72cm (0-8.9 cm). Comparisons of the mean of pre and post chemotherapy diameters showed a significant difference with p value <0.001.

The level of agreement between CBE and USS for tumor size and lymph node status was 60% (Kappa 0.063) and 91.6% (Kappa 0.405)

Table 1. Demographics and clinic-pathologic characteristics

Characteristics	Mean (SD)	Number	Percentage
Side of tumor			
Right		60	50
Left		60	50
Duration of lump (months)	9 (± 7)		
Age range			
25 – 29		2	1.7
30 – 39		38	31.7
40 – 49		48	40.0
50 – 59	44.17 (± 9.07)	22	18.3
60 – 69		8	6.7
> 70		2	1.7
Weight	71.73 (± 15.9)		
Height	1.64 (± 0.07)		
BMI	26.68 (± 5.56)		
Age at menarche	14.71 (± 2.41)		
Parity			
Nulliparous		2	1.7
Multiple		118	98.3
Contraceptive use			
Yes		16	14.4
No		104	85.6
Pre-menopause		82	68.3
Post-menopause		38	31.7
Breast cancer stage			
IIb		6	5.0
IIIa		24	20.0
IIIb		62	51.7
IIIc		28	23.3
Histology types			
IHC (72 patients)			
ER +		24	33.3
ER –		48	66.6
PR +		12	16.7
PR –		60	85.7
Her2Neu +		42	58.3
Her2Neu -		30	41.7

Table 2. Breast ultrasound scan findings of malignant lumps

Characteristics	Mean	Number (%)
Tumor diameter (cm)	6.26 ± 2.42	
Lesions		
Solitary		78 (65)
Multiple		42 (35)
Tumor staging		
T2		16 (13.3)
T3		16 (13.3)
T4		88 (73.3)
Nodal status		
Present		108 (90)
Absent		12 (10)
Location of breast tumor		
LOQ		64 (53.3)
LIQ		50 (41.7)
UOQ		110 (91.7)
UIQ		62 (51.7)
Peri areolar involvement		90 (75)
Sonology descriptions		
Hypoechoic		78 (65)
Complex(Cystic/Solid)		42 (35)
Punctate Micro-calcification		104 (86.7)
Spiculated margins		62 (51.7)
Well circumscribed		32 (26.7)
Poorly circumscribed		88 (73.3)
Vascularity(increased)		82 (68.3)
Posterior acoustic shadowing		80 (90)
Posterior enhancement		46 (38.3)
Skin edema		88 (73.3)
Skin Thickening (cm)	7.24 ± 2.44	

Table 3. The mean diameters of pre and post chemotherapy diameters in CBE and USS

Assessment method	Mean tumor diameter (cm)	*p* value
Clinical breast examination	Pre- 11.43 ± 4.42 Post- 8.09 ± 2.08	
Ultrasound	Pre-6.26 ± 2.42 Post- 2.82 ± 1.72	< 0.001

respectively. Using the UICC criteria, partial response was noted in 100 (83.3%) patients and complete response in 6 (5%), while 8 (6.7%) and 6 (5%) had stable and progressive disease respectively. Parity was noted to be associated with tumor response (p-0.014) with stable disease in all nullipara and complete/partial response seen in women with two or more children (90.2%). We found no association between menopause, tumor grade, nodal grade, tumor stage or immunohistochemistry status and response to NAC. Of importance is that all patients with no axilla metastasis had complete response (p = 0.008) to chemotherapy. No tumor greater than 5 cm demonstrated complete response (p = 0.95). In comparing the pre-chemotherapy mean tumor diameter between responders (partial/complete) versus non-responders (stable or disease progression); it was higher in non-responders (7.84 ± 2.77cm) than in non-responders (6.05 ± 2.32cm), although this was not statistically significant (p-0.07). In multiple logistic regression analysis, none of the selected variables was a positive predictor of tumor response to NAC.

Discussion

Collaborative meta-analysis on outcome of use of anthracycline based chemotherapeutic (AC) regimen showed superiority over the traditional Cyclophosphamide-Methotrexate and 5Fluoro-uracil regimen (CMF) combination by demonstrating a reduction of the annual breast cancer death by 38% for pre-menopausal women and 20% for post-menopausal women [16] in women placed on the AC regimen. Studies have shown that palpation (CBE) overestimates the number of remission- either complete or partial relative to radiologic assessment while pathologic assessment is regarded as the gold standard in assessing response to neo-adjuvant chemotherapy [5]. The proliferative function of breast tumor represented by KI-67 is expressed differently in pre-chemotherapy versus post-chemotherapy samples and anthracycline treatment results in a significant decrease of mitotic activity [17-19]. Thus, a decreased KI-67 expression is not just a monitor of response to treatment but also an independent predictor of response to anthracycline based chemotherapy [5].

Our findings of two-thirds having intermediate or high-grade disease and a concomitant response to NAC buttress the findings by Wang et al that high mitotic count lesion had more significant response than tumors with lesser mitotic count [20]. The pathogenesis for this being the hyper proliferative state which renders the tumor more sensitive to Anthracycline chemotherapy and clinical implication is that it renders them more susceptible to the structural damage induced during DNA synthesis, thus leading to a decreased viability of newly formed cells [21-23]. Although the molecular subtypes was obtained in two-thirds of patients, we found no association between the molecular subtypes (ER/PR/Her2) and response to NAC, however the basal-like (ER/PR/Her2 negative) patients manifested stable disease or partial response more, this is in keeping with reports from other parts of the world that basal-like (ER/PR/Her2 negative) breast carcinoma are more sensitive to anthracycline based chemotherapy [5,10,24]. There have been conflicting reports about Her2/neu expression as a predictor of response to anthracycline chemotherapy [5,24,25]; In this study, we found no association between Her2/neu expression and response to NAC. The in-vivo response of a tumor generally reflects its chemo-sensitivity and if the response truly reflects the sensitivity of all tumor burden, both loco-regional and micro-metastases, the response should be positively correlated with outcome [5]. Most authors find no association between clinical/ pathologic response and outcome (disease free survival and overall survival) [5,26].

The common ultrasound features of malignancy noted in another study [27] was also found in at least two-thirds of recruited patients and were consistent with the ''BIRADS'' descriptor [28] for malignant breast masses. A spiculated margin in the setting of an irregular shaped mass has indeed been noted to have a positive predictive value in about 62-85% range for malignancy [27], of which our findings fall within the quoted range. In our study, ultrasound was able to detect more multifocal/ multicentric disease in up to a third of patients when clinical breast examination showed unifocal disease at the pre-chemotherapy assessment stage; this is clearly higher than in a previous review [8] where only an additional 10% was discovered in their study subjects. One explanation for missing such a substantial number is that peri-tumoral edema and skin involvement mask or reduce proper delineation of other satellite lumps in the ipsilateral breast, thereby causing over estimation of the tumor size clinically. Indeed, the same reasons explain the significant difference in the mean tumor size measured in favor of by CBE over USS. Of note also, is the relevance of excessive posterior acoustic shadowing of the tumor on ultrasound scan which may reduce visualization of the posterior margins of the tumor. Axillary nodal staging was missed in 5% of patients by CBE, this was clearly picked up by USS, this further buttressing the advantage of ultrasound over CBE in the clinical staging of patients. Our study findings on tumor staging between CBE and USS align with the findings of Sperber et al. [8] while Yeh et al. [29] reported a lower level (48%) of agreement between CBE and USS in their series. The down-staging of an additional 10% of stage III cancer to stage II in our study demonstrates the superiority of USS to CBE in assessment

of patients' response to treatment. Subjective tumor responses that were not measurable in the post-chemotherapy setting were improved tumor margin delineation noted in figures 1 and 2 respectively.

The superiority of the USS in delineating breast lumps than mammography is clear in the pre-chemotherapy setting than in the post-chemotherapy size assessment setting [30-33]. The implication in a setting where LABC is the norm [33-35], is that initial staging by a verified tool (USS) ensures proper staging and need for neo-adjuvant treatment or not. From a previous work, only a negligible fraction of our patients received breast conserving surgery (BCS) [7], whilst BCS is the gold- standard in developed parts of the world. Reasons for this are that in such parts of the world, most tumors are screen detected and are early stage disease. The efficacy of BCS viz-a-viz modified radical mastectomy (MRM) in early breast cancer has long been established [36-39]. Important findings in our study militating against BCS is the involvement of the nipple-areolar complex, demonstrated in three-quarter of patients by ultrasound; which contrasts sharply with the less than a fifth quoted in a previous study [40], so also, the increased diagnosis of multi-centric disease by ultrasound when compared to CBE. The level of correlation between CBE and USS nodal staging tallied with previous findings [8]. Overall, we found that the greater the nodal disease burden, the less the response to chemotherapy. There was no significant association between the histologic grade, tumor stage or immunohistochemistry and the response to NAC, as was noted previously [40]. Following NAC, the non-measurable (subjective) response noted in our study subjects were akin to the findings by Kumer et al. [41], and these included improved tumor margins definition and reduction in skin edema. Our study results compare favorably with earlier epochs both within the sub-region and in Europe [42,43] in terms of response using the RECIST criteria [15].

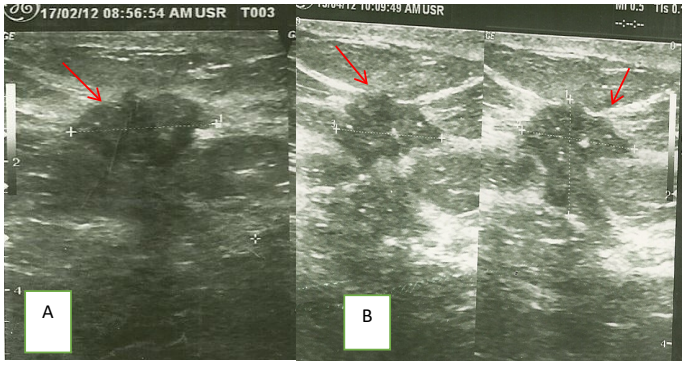

Figure 1. (A) Pre and (B) Post- chemotherapy ultrasound images of a patient's improved definition of tumor margin (arrows) after two cycles of chemotherapy

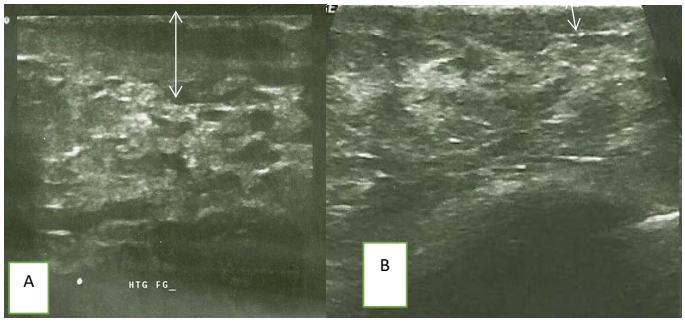

Figure 2. (A) Pre and (B) Post- chemotherapy ultrasound images of another patient demonstrating reduction in skin thickness (arrows) after a course of chemotherapy

Limitations

The gold standard modalities (pathologic response and Breast magnetic resonance imaging) in assessing response to neo-adjuvant chemotherapy were not done in this study because of cost. Lack of routine analysis of patient's hormonal receptor status (immunohistochemistry) was also noted.

Conclusion

Anthracycline based NAC has been shown to be effective sonographically in downstaging LABC in our setting whilst the breast ultrasound scan is a cheap and veritable diagnostic radiological tool in tumor and nodal staging while also assessing more effectively the response to NAC when compared to CBE.

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