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Sonographic patterns of infra and supra-clavicular malignant lymph nodes in breast cancer patients at the Uganda cancer institute. A cross-sectional study.

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Abstract

Background

At the Uganda Cancer Institute, the sonographic protocol for breast imaging in malignancies mainly focuses on the breast itself and level I axillary lymph nodes. Axillary Level II, level III plus supraclavicular ultrasound scans are not routinely requested and yet are vital in early detection of lesions even before they become clinically apparent.

Methodology

This was a hospital based cross-sectional study involving 378 breast cancer patients who were randomly sampled. Those with dual malignancies were excluded. Clinical evaluation of the breasts, the axilla, the sub-clavicular, the infra and supra clavicular areas was performed followed by sonographic examination by experienced sonographers and imaging technologists.

Results

Infraclavicular and supraclavicular sonographicaly malignant lymph nodes ranged from 0.13-3.8 cm in length with a mean of 2.2 cm. Most of the lymph nodes 58% maintained their oval shape and had changes in other areas such the capsular margins (45% being irregular), cortex thickened (71.8%), unclear corticomedullary boundaries (71.3%) hilar thinning, (68.5%), calcifications (21%), necrotic changes (27.6%), and presence of flow on color Doppler which when combined together, fit our criteria for classification of lymph node as malignant. Level V (the posterior triangle of the neck) had 47.4% of the supraclavicular lymph nodes.

Conclusion

The commonest stations for supraclavicular malignant lymph nodes were Level V (the posterior triangle of the neck). The presence of flow, possession of unclear corticomedullary boundaries, thickening of the cortex were among the commonest patterns in the malignant lymph nodes.

Recommendation

All medical imaging professionals particularly those doing sonography on cancer patients and suspected cancer patients should start including the scanning of axillary levels II, III and the supraclavicular areas (at least level V, III and VII) in their protocols in addition to the normal scanning of the breast and axillary level I only.

Keywords: sonographic patterns, clavicular malignant lymph nodes, breast cancer, Uganda cancer institute
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Background

Non communicable diseases, cancer inclusive, have become a major health burden world over(Hjelm et al., 2019) accounting for over 10.08 million death in 2019 alone. Female Breast cancer is the commonest globally,(Rebol et al., 2020) but the second in Uganda after cervical cancer.(Gakwaya et al., 2008).

The recent therapeutic advances in oncology have led to improved survival and prolonged life expectancy for breast cancer patients, which also gives a greater chance of developing distant metastases (Rebol et al., 2020). Breast cancer metastases above the clavicle are called supraclavicular metastases. (Sesterhenn et al., 2006).

Studies have shown a 4.3% incidence of supraclavicular metastases in breast cancer and also notes that those with visceral metastases have a poor prognosis than those without (Rebol et al., 2020).

Following a clinical examination, suspicious cervical masses have to be investigated by imaging with tools like B-mode sonography, CT and MRI. Sonography of the neck has high sensitivity for the detection of enlarged lymph nodes (90–97%) and is superior to palpation and CT (Sesterhenn et al., 2006).

In Africa, where most of the countries are of low- and middle-income status (LMICs), with very few CT scanners per population density, the use of sonography for the detection of axillary, sub clavicular and infraclavicular plus the supraclavicular areas will help increase diagnostic accuracy of nodal metastatic/malignant breast lesions and also supplement on the data provided by 3D MPR- Imaging methods where available.

At the UCI, the leading tertiary hospital for diagnosing and managing breast cancer, there is no local data about the incidence/prevalence and sonographic patterns of malignant infra and supraclavicular lymph nodes among breast cancer patients hence the need for this study.

Objective

To determine the sonographic patterns of infra and supraclavicular lymph nodes in breast cancer patients at the Uganda cancer institute.

Methodology

Study type and study design

This was a hospital-based prospective cross-sectional study.

Study area and study setting

The study area was the Uganda cancer institute located in Kampala, Uganda's capital about 4 km north, from the city Centre.

Uganda Cancer Institute is a public specialized tertiary care medical facility owned by the Uganda Ministry of Health. It also houses the East African Centre of excellence for oncology. Its services include clinical oncology services, radiation oncology services, and surgical oncology services with diagnostic services in laboratory and medical imaging among others. It receives a total of about 800 breast cancer patients annually. In the oncology imaging unit, there is a single big bore Philips CT scanner and simulator equipment, a digital mammography equipment, a digital x-ray with fluoroscopy and 2 ultrasound scanner machines manned by a staff of 15 people which includes 4 radiologists, 7 radiographers/sonographers and 4 nurses. The ultrasound unit receives about 80 patients per day and in particular 3-7 patients are positive for breast malignancies according to the departmental records. The study was carried out at the Uganda Cancer Institute in between March and June 2024.

Study population

The study population was patients with a histological diagnosis of primary breast cancer presenting to the Uganda Cancer Institute.

Sampling technique

Random sampling technique of using sequentially numbered opaque sealed envelopes (SNOSE) was used. Opaque sealed envelopes were prepared and numbered accordingly and distributed based on the booking lists at various entry points. Those eligible to participate in the study were consented, and our study protocol was followed during the examination of these study participants.

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Inclusions and exclusion criteria

Inclusion criteria: All patients with a diagnosis of breast cancer malignancy, and a UCI file number presenting at the Uganda Cancer Institute.

Exclusion criteria: Those with dual malignancies.

Sample size

The sample size (N) was determined using a statistical formula suggested by Kish and Leslie (1965) as expressed below;

$$n = \frac{z^2 p\,(1-p)}{d^2}$$

Where N= sample size
Z= standard deviation at 95% confidential level (i.e, 1.96)
P= prevalence (prevalence is not known for our population so we estimate it at 50% =0.5, therefore p=0.5)
d = acceptance degree of error (5%=0.05).

$$N = \frac{(1.96)^2 \times 0.5(1-0.5)}{(0.05)^2}$$

$$N = \frac{3.8416 \times 0.25}{0.0025}$$

N = 384 participants (to be adjusted for the study period)

Study variables

Dependent variables these were the presence of infraclavicular and supraclavicular lymph nodes.

Independent variables

Patient variables: Such as: age, sex, education level, region of origin, etc.
Clinico-pathological variables: the stage of cancer at diagnosis, history of receiving any cancer treatment, number of lymph node stations involved.

Data collection methods/technique

Patient recruitment

The recruitment was done through the multiple UCI entry points (navigation unit, breast clinic, imaging unit, and radiotherapy unit, etc.) where patients were educated about the study and written informed consent obtained from the study participants.

Clinical and sonographic examination

Training: Clinical and imaging personnel (sonographers, imaging technologists, radiologists and radiographers) underwent a training program to familiarize themselves with research protocol and data collection tool.
Equipment: High resolution ultrasound scan machine with 7-12 MHz transducer frequencies was used. Calibration of the equipment was done. The ultrasound scan equipment used was a Mindray M-6 model, manufactured by Shenzhen Mindray Bio-medical Electronics Co,. LTD in 2021 and installed the same year at the UCI.
Standardization: All sonographic examinations followed a standardized protocol to minimize variability.
Protocol: A standardized clinical examination of the breasts, and/or incision site (for post MRM patients), the axillary levels I, II and III plus the head and neck area were performed by a clinician and results documented on the questionnaires.
Ultrasonographic examination of the breast, axillary levels I, II and III plus the supraclavicular/neck were performed by experienced sonographers and imaging technologists with a minimum of 3 years' experience in oncology imaging and results were documented in the questionnaire.
Data recording: Patient information and all other findings were recorded by the clinicians, the radiographers, and imaging technologists involved in the study.

Data collection tool

The data collection tool comprised of a structured questionnaire.

Quality control

The data collection tool comprised a pre-tested questionnaire (within the UCI oncology imaging unit). All the necessary data was collected and checked for efficacy.
The questionnaires were coded and before completing the study, they were checked for missing data and consistency.
Complete QA (electrical and mechanical) was performed on both the ultrasound machines used.
Experienced clinicians, sonographers and imaging technologists (with a minimum of 3 years' experience in cancer work) were contracted.
Where there was a discrepancy in the findings, a second or third person was used to gain consensus.
Pre-testing of the data collection tool was done using 10 questionnaires by patients who were followed up from the

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navigation unit until to the imaging unit where the final part of the questionnaires was filled.

Data processing, analysis and presentation.

Questionnaires were sorted, edited, and categorized accordingly. Data was analyzed using Microsoft Excel. The results were scrutinized and presented in form of tables, bar charts, pie charts, and line graphs where applicable.

Ethical considerations

Permission and ethical approval to conduct the study was obtained from the research and ethics committee of Mengo Hospital.
Administrative approval was sought from the Uganda Cancer Institute research and Ethics committee under IRB Number SR-24.
Verbal and written consent out of free will was obtained from the study participants and all information obtained was kept confidential and for this reason, no study participant's names were written on the questionnaires.
No harm was afflicted to patients.

Results

Demographic characteristics and Clinico-pathologic history.

The study had 378 respondents, 99% were females with a male to female ratio of 1:75. The mean age of the participants was 45 years, and the median age was 39.5 years. Of all the participants, 74.7% were educated up to at least secondary school level. Other results are presented in the table 1.

Table 1 showing the social demographic characteristics of the participants.

No	Variable		Frequency	Percentage
1	Sex	Female	373	99.0
		Male	5	1.0
2	Age	>75 Years	6	1.6
		65-75 Years	43	11.4
		55-65	76	20.1
		45-55	114	30.2
		35-45	102	27
		25-35	37	9.8
3	Residence	Central	119	31.5
		Northern	105	27.8
		Eastern	83	21.9
		Western	71	18.8
4	Marital status	Married	136	36.0
		Cohabiting	94	24.9
		Widowed	68	17.9
		Divorced	49	12.9
		Single	31	8.2
5	Education level	Not educated	16	4.2
		Primary level	80	21.2
		Secondary level	169	44.7
		Tertiary level	113	29.9
6	Annual income	5-12 million	188	49.7
		<5 million	109	28.8
		12-24 million	58	15.3
		>24 million	23	6.1

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Respondents' clinico-pathologic History

Of all the 378 study participants, only 20.9% were newly diagnosed breast cancer patients while the remaining 79.1% were old patients on continuing therapy or clinical follow up. Up to 20% of the participants didn't know their family history of breast cancer, only 37.8% knew and had a positive family history of breast cancer.

Table 2 showing the clinico-pathologic history of the study participants

No	Variable		Frequency	Percentage
1	Family History of breast cancer	Yes	143	37.8
		No	157	41.5
		Don't know	78	20.6
2	Time taken from noticing symptoms to getting medical diagnosis.	<1 Month	21	5.5
		1-3 months	92	24.3
		3-6 months	148	39.2
		6-12 months	75	19.8
		>12 months	42	11.1
3	Stage of cancer at diagnosis	stage IV	74	19.6
		Stage IIIC	72	19.3
		Stage IIIB	99	26.1
		Stage IIIA	64	16.9
		Stage IIB	9	2.4
		Stage IIA	3	0.8
		Stage I	0	0
		Stage	0	0
		Unknown	56	14.8
4	Primary Histologic diagnosis n-375	Invasive ductal carcinoma	321	97.1
		Lobular carcinoma	36	9.5
		Others	10	2.6
		Clinical Diagnosis	3	0.8
5	Histological grading n-375	Poorly Differentiated	199	53.1
		moderately differentiated	123	32.8
		Well differentiated	53	14.1
6	Treatment type received by patients n-299	Chemotherapy+ radiation	127	42.5
		Chemo-radiation + surgery	85	28.4
		Chemotherapy/Hormonal therapy alone	49	16.4
		Chemotherapy + surgery	38	12.8
		Surgery only	0	0
		Radiotherapy alone	0	0

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Sonographic patterns of infra and supraclavicular lymph nodes in breast cancer patients.

Lymph node sizes: Most of the lymph nodes sizes ranged from 0.1 cm to 3.8 cm in length with a mean size of 2.2 cm. These included the lymph nodes that qualified as benign and those that met the characterization criteria for malignancy. The benign lymph nodes were typically below the size of 2 cm, while the malignant ones ranged from 0.13-3.8 cm. Other lymph node characteristics on sonography are shared in the table 3.

Table 3 showing lymph node characteristics

l	Variable		No. Of LN Stations	% age of LN Stations
		oval	124	58.2
		Round	51	23.9
a)	Shape of lymph nodes	Irregular	38	17.8
	Lymph node capsular	Smooth sharp margins	117	55.0
b)	margins	Ill-defined margins	96	45.0
	Thinning/loss of hilar	Yes	146	68.5
c)	architecture	No	67	31.5
		Eccentric/concentric thickening of cortex	153	71.8
d)	Thickening of the cortex	Normal cortex	60	28.2
	Presence of unclear	Yes	152	71.3
	corticomedullary			
e)	boundaries	No	61	28.7
	Presence of intranodal	Yes	45	21.0
f)	calcifications	No	168	79.0
	Presence of	Yes	59	27.6
g)	necrosis/cystic changes	No	154	72.4
		No flow on Color flow imaging	32	15.2
		Mixed (central and peripheral flow)	87	41.0
		Peripheral flow	45	21.3
		Central flow	12	5.5
h)	Vascularity (type of flow)	Other (Collaterals blood vessels,	36	17.0
		Mixed (high and low resistance arterial waveform)	82	45.1
		high resistance waveform	66	36.7
i)	Type of flow n-181	Low resistance waveform	33	18.2

Lymph node Characterization for malignancy and location of supraclavicular lymph nodes by neck levels

The criteria of considering any lymph node with at least 3 of the characteristics that favor malignancy as being malignant (Ai et al., 2020) was used. The key variables were; shape, boundaries, hilar architecture, intranodal calcifications, capsular margins, corticomedullary boundaries, cortex thickening, adjacent organ invasion and presence plus type of vascularity. 320 lymph node stations among 186 patients were found to contain lymph nodes that met the characterization criteria for malignant lymph nodes. This is

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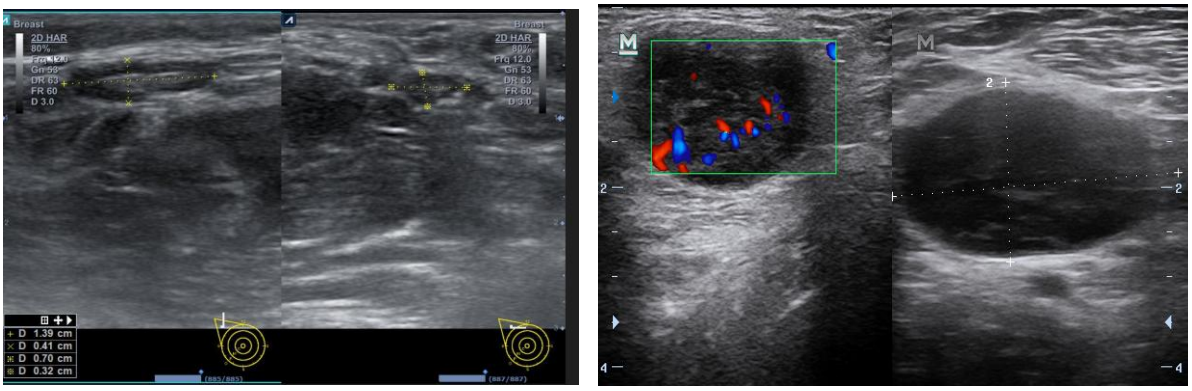
because some patients had malignant lymph nodes in more than one station only.

Table 4 Shows the Number of Patients with Malignant Lymph nodes and The Location Of Supraclavicular Lymph Nodes (Stations) By Neck Regions.

No. of patients with malignant lymph nodes					Location of supraclavicular Lymph nodes (Stations) by neck region		
Lymph node station	Stations with Malignant L. Nodes	Frequency	Percentage		Neck Level	No. Of Malignant L. Nodes	Cumulative frequency
Axillary level I only	44	44	23.7		Level I	0	0
Axillar level II only	3	3	1.6		Level II	3	3
Axillary level I & II	102	51	27.4		Level III	11	14
Axillary level III	5	5	2.7		Level IV	0	14
Axillary level I, II and III	201	67	36.0		Level V	20	34
Supraclavicular region	7	7	3.8		Level VI	0	34
Axillary levels I, II, III & IV	36	9	4.8		Level VII	9	43
Total:	320	186	100			43	

Fig.1 Sample Ultrasound Image of Benign and Malignant Lymph Node From the Study



(L) ultrasound image of one of the lymph nodes with characteristics of being benign (Oval, regular capsule, with a prominent central echogenic hilum etc.) and (R) an ultrasound image obtained from level I axilla showing characteristics of malignant lymph nodes (large, irregular capsule, no central echogenic hilum, no clear corticomedullary boundaries, with color flow on Doppler etc.)

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Discussions

Demographics

Gender: 98.9% of the respondents were females. This shows that breast cancer is more common in females than in males. This is consistent with most of the studies including one done by,(Rebol et al., 2020), (Ma et al., 2020)·(Nauroth et al., 2017) and statistics by WHO.

Age of respondents: The mean age of the breast cancer patients in this study was 45 years which is the same with the findings of (Gakwaya et al., 2008), but the median age was 39.5 years. The peak age differed where breast cancer is highest among those aged between 45-55 years in our study unlike in (Gakwaya et al., 2008), study where it was 30-29 years.

Residence of respondents by regions: Most of the respondents were from the central region (31.5%), with the least being the western part of Uganda 18.8%. This maybe because of the reasons cited by (Hjelm et al., 2019) that, the people from the central part of Uganda are more likely to get breast cancer care compared to other regions since most of the tertiary healthcare services are located in the central part of Uganda giving them ease of access.

Respondents Clinico-pathologic history

Family history of breast cancer: The study showed that up to 20.6% of the study respondents were not sure of the family history of breast or any other cancers among their close relatives. This shows that people do not disclose to their relatives once they are suffering from cancer, an aspect that can still be linked to stigma over the diagnosis of cancer.

Time taken from discovery of symptoms to seeking medical attention: Only 29.8% of our study respondents managed to show up early (<3 months of noticing signs) for diagnosis. This can be attributed to the low awareness levels among the Ugandan population as discussed by(Hjelm et al., 2019) and the cultural/religious beliefs surrounding the cancer diagnosis.

Stage of cancer at diagnosis: Subsequently only 3.2 % of the cancer patients were diagnosed early at stage II. The rest were late stage diagnosis which is consistent with the finding of (Gakwaya et al., 2008), (Ma et al., 2020) about the late stage diagnosis of breast cancers in the Ugandan setup.

Primary histologic diagnosis of breast cancer: The most prevalent histological diagnosis was infiltrative ductal carcinoma. This is in agreement with most of the studies done earlier by (Gakwaya et al., 2008), (Ma et al., 2020). Clinical diagnosis for breast cancer is still being used especially in cases where histological diagnosis has proved negative, but clinically and radiologically, the condition meets the characterization of a cancerous lesions.

Histological grading: Poorly differentiated adenocarcinoma is the most prevalent cancer grade, followed by moderately differentiated, findings which are in agreement with studies of (Gakwaya et al., 2008).

Treatment received by study respondents. Chemotherapy and radiotherapy were the most prevalent modes of treatment accounting for up to 42.5% of all the respondents. These are common treatment modalities in late-stage breast cancers, unlike surgery which is very beneficial in early stage. This can be attributed to the scarcity of breast surgeons who are mainly in Kampala (Hjelm et al., 2019) and the late diagnosis of breast cancers in Uganda which doesn't necessitate mastectomy due to metastatic spread by the time of diagnosis. New patients (Patients who had never got any of the cancer treatment modalities were only 20.9%.

Sonographic Patterns of infra and supraclavicular lymph nodes in breast cancer patients.

Lymph node size: Most of the malignant lymph nodes ranged from 0.1-3.8 cm in length with a mean size of 2.2 cm, findings which are in agreement with (Sesterhenn et al., 2006) who further agreed that modern ultrasound technology can detect smaller than 0.1 cm lymph nodes.

The shape of the malignant lymph nodes in the various stations varied significantly from the normal oval shape to round and irregular. The lymph node capsular margins varied from the normally smooth and sharp to having ill-defined/invasive margins, consistent with the findings of (Ai et al., 2020). Thinning/loss of hilar architecture (68.5%), the thickening of the cortex (71.8%) and possession of Unclear corticomedullary boundaries (71.3%) were among the commonest findings in the malignant lymph nodes in our

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study. This is in agreement with the studies by (Ai et al., 2020), (Nauroth et al., 2017).

Intranodal calcifications and Necrosis/cystic changes were relatively rare at 21.0% and 27.6% respectively. The reason is not yet clear.

Vascularity of lymph nodes. Most of the lymph nodes (84.9%) demonstrated flow on color and power Doppler imaging with 41% showing a mixed flow profile (Mixed central and peripheral flow) and collateral blood vessels, subcapsular vasculature, aberrant vessels accounting for 17%. On pulsed Doppler, mixed high and low resistance arterial spectral Doppler waveforms contributed highest with 45.1% with isolated low resistance waveform only accounting for 18.2%. These findings are consistent with the findings that favor malignancy which include; peripheral/mixed peripheral: central blood vessels, high resistance waveform, RI >0.8, PI >1.5, aberrant vessels: displaced parent vessels, sub-capsular vasculature, non-perfused areas, and non-tapering vessels. In malignant lymph nodes, the increase in resistivity of a node is attributed to increased cellularity within an infiltrated lymph node. This is different for those with necrotic changes. (Ai et al., 2020).

Location for supraclavicular lymph nodes by neck levels.

Our results found out that the commonest stations for supraclavicular/neck malignant lymph nodes were; Level V (the posterior triangle of the neck), with 47.4%, followed by level III (medio-jugular group) with 23.7%, then level VII (lymph nodes in the anterior superior mediastinum and tracheoesophageal grooves). There were no malignant lymph nodes detected in the jugular levels as discussed by (Nauroth et al., 2017) during their study. Still in this study, it shows the localization of neck metastases to the neck regions as being highest at level V with 66.6%, then followed by level III with 33.3%. Though the percentages are not similar to this study, the pattern is similar. (Nauroth et al., 2017).

Study limitations

There was a referral bias risk in this study in that it was done at the Uganda cancer institute an institute that receives late-stage referrals from other facilities and the information got may not appeal to the general prevalence levels of the entire population.
The inability to sample lymph nodes for histologic correlation with ultrasound.
Some patients had undergone various treatment modalities for breast cancer, an aspect that could have affected the prevalence.
The inadequate finances which only allowed for a cross-sectional study whose results was only used to estimate and not confirm the prevalence of supraclavicular lymph nodes in breast cancer patients.

Conclusions

The Prevalence of infraclavicular malignant lymph nodes was 44.9%, and that of supraclavicular malignant lymph nodes was 4.2%.
The commonest stations for supraclavicular malignant lymph nodes was Level V (the posterior triangle of the neck).
The presence of flow, possession of unclear corticomedullary boundaries, thickening of the cortex and thinning/loss of hilar architecture were among the commonest patterns in the malignant lymph nodes.

Recommendations

Recommendations to research:

More research needs to be carried out in the following areas:
A study on the incidence of infraclavicular lymph nodes among breast cancer patients.
A study correlating histology, histological grades and receptor status with sonographic findings in infra and supraclavicular lymph nodes in breast cancer patients.
Studies correlating CT scan to sonographic findings in assessing for infra and supraclavicular lymph nodes.

These studies will help broaden the knowledge base with scientific evidence in the field on breast oncology imaging and lymph node detection using ultrasound.

Recommendation to practice:

Since most of our patients present late, and despite the high prevalence of infraclavicular malignant lymph nodes in our setup, all medical imaging professionals particularly those doing sonography on cancer patients and suspected cancer patients should start including the scanning of axillary levels

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II, III and the supraclavicular areas (at least level V, III and VII) in their protocols in addition to the normal scanning of the breast and axillary level I only.

Recommendation to policy makers:

To allocate funding for more research in this area of cancer diagnosis as sonography is cheap, readily available and can help in staging and early treatment decisions which in turn lead increased chances of survival for breast cancer patients.

List of abbreviations and acronyms

AJCC: American Joint Committee on Cancer
BMI: Body Mass Index
CNS: Central Nervous System
CT: Computed Tomography
DCIS: Ductal Carcinoma in situ:
DMFS: Distant metastatic free-survival
EDV: End-Diastolic Velocity
FDG: Fluorodeoxyglucose
ISLM: Ipsilateral supraclavicular lymph node metastases.
LMICs: Low and middle income status countries.
MHz: Mega Hertz
mISLM: Metachronous Ipsilateral supraclavicular lymph node metastases.
MPR: Multi-planer reconstructions.
MRI: Magnetic Resonance Imaging
NCDs: Non-communicable diseases
NLNM: Neck lymph node metastases
OPD: Out Patient Department
OS: Overall survival.
PET: Positron Emission Tomography
PI: Pulsatility Index
PSV: Peak Systolic Velocity
RI: Resistive index
sISLM: Synchronous Ipsilateral supraclavicular lymph node metastases
SLNM: Supraclavicular lymph node metastasis
SNOSE: Sequentially sampled opaque sealed envelopes
STC: Solid Tumor Centre
THI: Tissue Harmonic Imaging
TNM: Tumor Node Metastasis
UCI: Uganda Cancer Institute
US: Ultrasound.

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Conflict of interest

The author declares no conflict of interest

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Data availability

Data is available upon request

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