J Nepal Health Res Counc 2023 Jan-Mar;21(58): 71-5

Correlation of Imaging Findings with Molecular Subtypes of Breast Cancer

Om Biju Panta,[1] Vivek Dhakal, [1] Bibek Gurung,[1] Ram Kumar Ghimire[1]

[1]Department of Radiology and Imaging, Nepal Mediciti Hospital, Lalitpur, Nepal.

ABSTRACT

Background: Ultrasound and Mammography are first-line imaging in breast cancer. The management of malignant breast lesions depends on molecular biomarkers in the tumor cells. This study aims to correlate different imaging findings in breast carcinoma with immune-histology subtypes.

Methods: The study was a retrospective study conducted between 2018 January to 2021 December. Patients with malignant breast lesions who underwent USG-guided biopsy of breast lesions were included in the study. Ultrasound and mammographic findings of these patients were retrieved in PACS and analyzed. Malignant breast lesions were classified according to molecular markers into Luminal A, Luminal B, Her- 2 enriched, and triple-negative breast cancers. The correlation between imaging findings and molecular subtypes of breast cancer was analyzed.

Results: A total of 42 patients were included in the study. The mean age of the patients in our study was 52.24+/-13.54 years with median of 51 years (IQ range-19.5 years). The most common IHC subtype was Luminal type B (22, 52.4%), followed by triple negative (15, 35.7%), luminal type A (4, 9.5%) and least common was Her-2 enriched (1, 2.4%). Mammogram was non-diagnostic in 9.5% of case. Oval shape and well marginated margin in ultrasound were more frequently associated with triple negative breast cancer than other subtypes ($P<0.05$). Rest of the characteristics of triple negative and other malignancies were not significantly difference in our study. No significant difference is noted between mammographic findings between various subtypes.

Conclusions: Triple negative breast cancer was more common in our population than in the west. Triple-negative breast cancers are more frequently well-defined and oval in shape mimicking benign lesions.

Keywords: Breast cancer; mammography; molecular subtypes; ultrasound

INTRODUCTION

Breast cancer is the third most common malignancy in the world and the second most common malignancy in women in Nepal.[1] Ultrasound and Mammogram are the first lines of imaging in breast lesions. Imaging findings can be used to characterize breast lesions according to the risk of malignancy and also guide the management of the lesions. The management and prognosis of malignant breast lesions largely depend on the molecular biomarkers in the tumor cells i.e. ER, PR, and Her-2 receptor status and Ki 67 when Her-2 is negative or equivocal.[2] According to the receptor status, malignant breast lesions can be classified as Luminal A, Luminal B, Her-2 enriched triple-negative/basal subtypes. Management and prognosis of the lesions are different according to these subtypes.[3] Few studies correlating mammographic and ultrasound findings in breast cancer with various subtype of breast cancer has been published worldwide, however no such study has been reported in Nepal. This study aims to correlate different mammographic and ultrasound findings in breast carcinoma with the immunohistology subtypes.

METHODS

The study was a retrospective study conducted between 2018 January to 2021 December. Patient who underwent USG guided biopsy of breast lesions in the department and that proved to be malignant were included in the study. The ultrasound images and mammographic images of the patients were retrieved from picture archiving and recording system and were read by two radiologists with 4 and 6 years of experience in breast imaging. Ultrasound and Mammographic findings were recorded according to Breast Imaging-Reporting and data system (BI-RADS) lexicon. Biopsy findings of the patients and their immunohistochemistry findings were retrieved. The breast lesions were classified as Luminal A, Luminal B, Her-2 enriched and triple negative. Data analysis was

Correspondence: Dr Om Biju Panta, Department of Radiology and Imaging, Nepal Mediciti Hospital, Lalitpur, Nepal. Email: bijupanta@yahoo.com, Phone: +9779842877382.

done by using SPSS 21.0. Categorical variables were presented as percentage and numeric variable were presented as mean and standard deviation. Correlation of ultrasound and mammographic findings according the immunohistochemical types was assessed by using chi square test.

RESULTS

A total of 42 patients were included in the study who underwent Ultrasound guided breast biopsy and were proven as malignant breast lesions by histopathology. Ultrasound of all patients could be retrieved in the PACS, however mammogram of only 24 patients were retrieved from PACS.

The mean age of patient in our study was 52.24+/-13.54 years with median of 51 years (IQ range-19.5 years). Maximum age of the group was 81 years and minimum age was 24 years. The lesions were classified as BIRADS 3 and 4 (21, 50%) and BIRADS 5 (21, 50%) on ultrasound. On Mammography 4(9.5%) lesions were BIRADS cat 0, 11(26.2%) lesions were BIRADS cat 3 and 4 and 9(21.4%) lesions were BIRADS Cat V. Ultrasound characteristics of lesions are given in table 1.

Table 1. Ultrasound characteristics of malignant breast lesions

Ultrasound Characteristics	Number (%)	Remarks
Shape: Oval Irregular	 15(35.7%) 27(64.3%)	
Margin: Ill Marginated Well Marginated	 29(69%) 13(31%)	Ill marginated includes- spiculated, microlobulated, illdefined and angulated margins
Calcifications Present Absent	 9(21.4%) 33(78.6%)	
Posterior Features Enhancement Shadowing None	 3(7.1%) 7(16.7%) 32(76.2%)	
Echopattern Hypoechoic Heterogeneous Mixed Solid Cystic	 40(95.2%) 1(2.4%) 1(2.4%)	
Orientation Parallel Antiparallel	 37(88.1%) 5(11.9%)	
Suspicious Axillary Lymphnode	13(31%)	

The most common IHC subtype was Luminal type B (22, 52.4%), followed by triple negative (15, 35.7%), Luminal type A (4, 9.5%) and least common was Her-2 enriched (1, 2.4%). There was no significant difference between various IHC subtypes in ultrasound findings in our study (Table 2).

Table 2. Mammographic characteristics of malignant breast lesions

Characteritics	Number (%) N=24	Remarks
Breast density A B C D	 5(20.8) 9(37.5) 7(29.2) 3(12.5)	
Mass Present Absent	 17(70.8) 7(29.2)	
Density of mass High Equal	 13(54.2) 4(16.7)	
Mass shape Oval/lobulated Irregular	 12(50%) 5(20.8)	
Margin Obscured margin Spiculated/irregular Well marginated	 8(33.3) 8(33.3) 1(4.2)	
Calcification Suspicious Benign None	 8(33.3) 1(4.2) 15(62.5)	5 suspicious calcifications were seen in asssociation with mass and 3 suspicious calcifications were seen without evidence of mass
Associated findings Present Absent	 3(12.5) 21(87.5)	Skin thickening was seen in 3 patients, nipple retraction was seen in one of the three patients.

The mean age of triple negative breast cancer was lower than rest of the group, however the difference was not statistically significant. Oval shape and well marginated margin were more frequently associated with triple negative breast cancer than other subtypes ($P<0.05$). Rest of the characteristics of triple negative and other malignancies were not significantly difference in our study (Table 3 and 4). No significant difference is noted between mammographic findings between triple negative and other subtypes of malignancy was noted (Table 5).

Table 3. Ultrasound characteristics of breast lesions according to immunohistochemistry subtype

Characteristic	Luminal A (N=4)	Luminal B (N=22)	Her-2 Enriched (N=1)	Triple Negative (N=15)	P- value
Shape					
Oval	1	6	0	8	0.325
Irregular	3	16	1	7	
Margin					
Ill marginated	3	17	1	8	
Well marginated	1	5	0	7	0.40
Orientation:					
Parallel	3	20	1	13	0.80
Antiparallel	1	2	0	2	
Echopattern					
Hypoechoic	4	21	1	14	
Hyperechoic	0	0	0	0	
Heterogeneous	0	1	0	0	0.84
Mixed	0	0	0	1	
Posterior features					
None	1	18	1	12	0.14
Shadowing	2	4	0	1	
Enhancement	1	0	0	2	
Calcification					
Present	2	5	0	2	0.42
Absent	2	17	1	13	
Axillary LN					
Present	2	5	1	5	0.79
Absent	2	17	0	10	

Table 4. Ultrasound characteristics of triple negative breast cancer compared with other subtypes

Characteristics	Triple negative (n=15)	Other subtypes (n=29)	P-value
Age	49.69+/-15.2	53.38+/-12.8	0.42
Lateratily			
Left	5(38.5%)	18(62.1%)	0.13
Right	8(61.5%)	11(37.9%)	
Shape			
Oval/lobulated	8(61.6%)	7(24.1%)	0.02
Irregular	5(38.5%)	22(75.9%)	
Margin			
Ill marginated	6(46.2)	23(79.3)	0.03
Well marginated	7(53.8)	6(20.7)	
Orientation			
Parallel	11(84.6)	26(89.7)	0.49
Antiparallel	2(15.4)	3(10.3)	
Posterior features			
None	10(76.9)	22(75.9)	0.25
Shadowing	1(7.7)	6(20.7)	
Enhancement	2(15.4)	1(3.4)	
Calcification			
Present	2(15.4)	7(24.1)	0.42
Absent	11(84.6)	22(75.9)	
Echopattern			
Hypoechoic	12(92.3)	28(96.6)	0.26
Others	1(7.7)	1(3.4)	
Axillary lymphnodes			
Present	5(38.5)	8(27.6)	0.36
Absent	8(61.5)	21(72.4)	

Table 5. Mammographic characteristic of triple negative breast cancer compared to others

Characteristics N=24	Triple negative N=8	Other subtypres N=16	P-value
Mammographic density			
A	3(12.5%)	2(8.33%)	
B	2(8.33%)	7(29.16%)	0.53
C	2(8.33%)	5(20.83%)	
D	1(4.16%)	2(8.33%)	
Mass present	5 (20.83%)	12 (50%)	
Mass density			
High	4 (16.66%)	9(37.5%)	0.82
Equal	1(4.16%)	3(12.5%)	
Mass shape			
Oval/lobulated	5 (20.83%)	7(29.16%)	0.08
Irregular	0	5(20.83%)	
Margin			
Obscured margin	4 (16.66%)	12(50%)	
Spiculated/irregular			0.11
Well marginated	1 (4.16%)	0	
Calcification			
Suspicious	1(4.16%)	7(29.16%)	0.12
Benign	1(4.16%)	0	
None	6(25%)	9(37.5%)	

DISCUSSION

Different molecular subtypes of breast cancer have different biological behavior and thus a variable prognosis with luminal A tumor (HR positive, Her-2 negative) having best prognosis whereas the luminal B

and triple negative having worst prognosis. Thus, it is imperative to determine the molecular subtype of breast cancer with biopsy before beginning the treatment and subjecting different subtypes to different hormonal therapy, chemotherapy and targeted therapy regimes.[2,3] The determination of molecular subtypes can only be done invasively by taking a biopsy, no imaging studies have been able to define molecular behavior of breast cancer till date. Our study analyses the ultrasound and mammographic character of biopsy breast cancer and tries to find the association with various molecular subtypes.

The proportion of triple negative breast and luminal B breast cancer was significantly higher in our study as compared to National institute of health data and previous international studies.[4,5] The incidence of triple negative is consistent with previous study reported from Nepal with incidence of triple negative cancer of ~ 32%, however incidence of luminal B is lower in previous study as compared to our study.[6,7] It is worrisome that incidence of triple negative breast cancer is seen higher in our country as it is associated with poor prognosis and higher mortality and recurrence. Also triple negative breast cancer is seen with patients with BRCA gene mutation, a higher incidence of triple negative breast cancer in our country might also be indicating high proportion of BRCA gene mutation. However, these studies were all single center study and doesn't however represent true picture of all breast cancer patients in Nepal. A multicentric study is needed to define the true picture of molecular subtype of breast cancer in Nepal.

Mammography was non-diagnostic in 9.5% of breast cancer patient, indicating the fact that mammography should be used in association with ultrasound in diagnostic workup of a palpable breast mass. This was due to dense breast obscuring lesions. Ultrasound proves to be a very useful modality in palpable breast lump in patients with dense breast. Other study has shown adjunctive ultrasound to be beneficial in high-risk screening with improved sensitivity on detection of lesions.[8]

Triple negative breast cancer was seen in slightly younger age group as compared to other subtypes of breast cancer; however, this finding was not statistically significant. Triple negative has been seen in younger population in prior studies as well.[4] The presence of basal-like cancer in younger population and association of triple negative cancer with basal like cancer in younger population was one of the explanation for the age dependent risk in younger women. On Ultrasound, triple negative breast cancers were more frequently well marginated and oval shaped as compared to other breast cancers which were ill marginated and had round or irregular shapes. On mammogram as well, triple negative cancers were more frequently lobulated as compared to irregular in other subtypes. These findings were also seen in previous study done comparing imaging findings of triple negative breast cancers.[9,10] These findings are defined as benign and less suspicious findings and are often followed up rather than biopsied. No other imaging features were different between various molecular subtypes.

There were several limitations in our study. The study was a single center study with small sample. Mammography reports of all patients were not available in PACS in our center further limiting data of mammography. We did not study newer molecular markers like PD L1 (Programed death Ligand 1), microsatellite instability (MSI) and BRCA gene mutation in our study.

CONCLUSIONS

Despite the limitations, we conclude that the proportion of triple negative breast cancers was high in our study and triple negative breast cancers also demonstrated well marginated and oval shape. We recommend a multicenter study preparing breast cancer database for the country. If the proportion of triple negative breast cancer is high as we found, BRCA mutation analysis to find genetic association of breast cancer in Nepal is highly recommended. We also recommend considering biopsy in well marginated and oval lesions (traditionally considered benign) due to poor patient compliance on follow up in our country and high prevalence of triple negative breast cancer.

CONFLICT OF INTEREST

The authors declare no conflict of interest

REFERENCE

1. Sapkota G, Poudel BR, Mallik DK, Wagle B, Dhakal S, Bhandari S. Prevalence of Breast Cancer in different geographical regions: A Retrospective Study from Central Nepal. Nepal J Cancer. 2022;6(1):101–5.[Google Scholar]
2. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022 Jun;20(6):691–722. doi:10.6004/jnccn.2022.0030
3. Johnson KS, Conant EF, Soo MS. Molecular Subtypes of Breast Cancer: A Review for Breast Radiologists. J Breast Imaging. 2021 Jan 1;3(1):12–24. doi:10.1093/jbi/wbaa110

4. Howard FM, Olopade OI. Epidemiology of Triple-Negative Breast Cancer: A Review. Cancer J. 2021 Jan;27(1):8–16.

5. Hwang KT, Kim J, Jung J, Chang JH, Chai YJ, Oh SW, et al. Impact of Breast Cancer Subtypes on Prognosis of Women with Operable Invasive Breast Cancer: A Population-based Study Using SEER Database. Clin Cancer Res. 2019 Mar 15;25(6):1970–9. doi:10.1158/1078-0432.CCR-18-2782

6. Khanal S, Singh YP, Sayami G, Ozaki A. Profile and Outcome of Triple Negative Breast Cancer at a Tertiary Care University Hospital in Nepal. Asian Pac J Cancer Care. 2020 Jun 7;5(2):101–5. doi; 10.31557/apjcc.2020.5.2.101-105

7. Hirachan S, Singh YP. Prevalence of Molecular Subtypes of Breast Cancer in a University Hospital of Nepal. J Inst Med Nepal. 2020 Apr 30;42(1):75.[Article]

8. Yamakanamardi S, Hiremath BV. Accuracy of mammography and sonomammography and its correlation with histopathology in the detection of breast cancer. Int Surg J. 2021 Jan 29;8(2):624. 10.18203/2349-2902.isj20210374

9. Ko ES, Lee BH, Kim HA, Noh WC, Kim MS, Lee SA. Triple-negative breast cancer: correlation between imaging and pathological findings. Eur Radiol. 2010 May;20(5):1111–7. doi:10.1007/s00330-009-1656-3

10. Anders CK, Carey LA, Burstein HJ. ER/PR negative, HER2-negative (triple-negative) breast cancer. UpToDate; Vora SR, Ed.; Wolters Kluwer: Waltham, MA, USA. 2021 Jan.[Article]