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Clinical Imaging of the Heterogeneous Group of Triple-negative Breast Cancer

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Abstract. *Background/Aim: Triple-negative breast cancer (TNBC) can be divided into subtypes of basal-like (BL), mesenchymal-like (ML), luminal androgen receptor (LAR), and immunomodulatory (IM). The aim of our study was to assess whether there are distinct radiologic features within the different TNBC subtypes and whether this has potential clinical impact. Patients and Methods: Imaging pictures of 135 patients with TNBC were re-evaluated. TNBC subtyping was performed on asservated tumor tissue using a panel of antibodies. Results: Mammographic margins of LAR-TNBC were more often spiculated (24.3% versus 0-4.1%). BL-TNBC presented more frequent a mass without calcification in mammogram than other subtypes (71.4% versus 48.6-57.9%). In ultrasound, ML and LAR were described more often with smooth borders. Conclusion: The histopathological subtype of TNBC influences its presentation in ultrasound and mammogram. This can reflect a different growth pattern of the subtypes and may have an impact on the early diagnosis of TNBC.*

Molecular typing led to a vast improvement in the diagnosis and treatment of breast cancer (BC) decades ago. Targeted therapy was developed for cancers with hormonal receptor positivity and for HER2 positivity, which significantly improved their prognosis. Lacking the three markers of estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor, triple negative breast cancer (TNBC) remains the most feared diagnosis with poor outcomes (1). TNBC is associated with younger age and a higher tumor stage at diagnosis, as well as BRCA 1 germline mutation (2). Today, TNBC is regarded as a heterogeneous disease. Subtyping provides further information about the molecular pathways, chemotherapy response, and the potential for development of targeted therapies (3). The TNBC subtypes have been classified into basal-like (BL), mesenchymal-like (ML), and luminal androgen receptor (LAR); lymphocytic infiltration defines a further subtype of immunomodulatory (IM) TNBC (3-5).

Early detection is crucial for the curative treatment of BC, especially for aggressive tumors. Mammography is considered to be the gold standard for screening of BC. In cases of dense breast tissue, family history of BC, and in women with suspicious findings in mammogram or clinical examination, additional ultrasound is indicated. For the objective assessment of breast lesions, the Breast Imaging Reporting and Data System (BI-RADS) has been established (6). Several features of mammographic and sonographic breast findings are evaluated algorithmically to minimize radiologist-dependent subjective ratings. TNBC is known to present more often benign characteristics in clinical imaging such as lobulated, oval-shaped, and circumscribed margins, than other types of BC (7). Benign classification and misinterpretation can lead to diagnostic delay and negative impact on the outcomes of BC (8). Despite TNBC subtypes having different therapy responses and outcomes, very little is known about their characteristics in clinical imaging. In this study we assessed specific features of TNBC subtypes in mammogram and ultrasound with the aim of improving the understanding of this heterogeneous disease.

Patients and Methods

Patients with TNBC who were diagnosed in the Breast-Center Zurich between 2002 and 2016 were included in the study. Patient- and disease-related data as well as outcome were evaluated retrospectively.

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Table I. *Patient and tumor characteristics*.

n	Overall 135	BL 49	IM 19	ML 30	LAR 37	*p*-Value
Age [y; mean (sd)]	57.7 (13.7)	55.3 (14.4)	54.7 (14.4)	57.0 (12.4)	62.9 (12.3)	0.07
Menopausal status (%)						0.02
Premenopausal	44 (32.6)	20 (40.8)	9 (47.4)	10 (33.3)	5 (13.5)	
Postmenopausal	91 (67.4)	29 (59.2)	10 (52.6)	20 (66.7)	32 (86.5)	
Reason for first consultation (%)						0.39
Self-detected palpable mass	80 (59.3)	35 (71.4)	12 (63.2)	18 (60.0)	15 (40.5)	
Screening	41 (30.4)	10 (20.4)	6 (31.6)	11 (36.7)	14 (37.8)	
Symptoms (discharge/pain)	5 (3.7)	1 (2.0)	0	1 (3.3)	3 (8.1)	
other	9 (6.7)	3 (6.1)	1 (5.3)	0	5 (13.5)	
Family history of breast cancer (%)						0.90
Yes	24 (17.8)	9 (18.4)	4 (21.1)	6 (20.0)	5 (13.5)	
No	110 (81.5)	40 (81.6)	15 (78.9)	24 (80.0)	31 (83.8)	
Unknown	1 (0.7)	0	0	0	1 (2.7)	
Histopathologic tumor size (%)						0.98
ypT0	5 (3.7)	2 (4.1)	1 (5.3)	1 (3.3)	1 (2.7)	
ypT1	19 (14.1)	6 (12.2)	5 (26.3)	4 (13.3)	4 (10.8)	
ypT2-4	8 (5.9)	2 (4.1)	1 (5.3)	3 (10.0)	2 (5.4)	
pT1	45 (33.3)	16 (32.7)	8 (42.1)	10 (33.3)	11 (29.7)	
pT2-4	58 (43.0)	23 (46.9)	4 (21.1)	12 (40.0)	19 (51.4)	
Histopathologic axillary lymph node (%)						0.44
ypN0	13 (9.6)	5 (10.2)	4 (21.1)	1 (3.3)	3 (8.1)	
ypN1-3	14 (10.4)	3 (6.1)	3 (15.8)	4 (13.3)	4 (10.8)	
pN0	77 (57.0)	30 (61.2)	10 (52.6)	19 (63.3)	18 (48.6)	
pN1-3	31 (23.0)	11 (22.4)	2 (10.5)	6 (20.0)	12 (32.4)	
Tumor grading (%)						0.05
Well differentiated (G1-2)	21 (15.6)	4 (8.2)	3 (15.8)	3 (10.0)	11 (29.7)	
Poor differentiated (G3)	114 (84.4)	45 (91.8)	16 (84.2)	27 (90.0)	26 (70.3)	

At patient's first presentation, initial evaluation had been performed and documented by trained breast radiologists in the Breast-Center Zurich. Standardized mammogram had been performed in two imaging planes (mediolateral oblique and craniocaudal). Ultrasound with 5-12 MHz transducers had been performed according to the BI-RADS guidelines. For classification reassessment, mammogram and ultrasound pictures were retrospectively reviewed by two experienced breast radiologists who were blinded for the patient's history and histopathological subtyping of the tumor. Radiological tumor characteristics such as margin, shape, orientation, echo pattern, and posterior features were categorized according to the BI-RADS classification. To analyse potential factors for misdiagnosis, the initially given BI-RADS classification (benign/probably benign *versus* probably malignant) was not changed but correlated to imaging features.

At initial diagnosis, surgical and biopsy specimens had been processed as formalin-fixed, paraffin-embedded tumor tissues according to the standardized protocol of the Department of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland. TNBC had been defined as expressing less than 1% of ER and PR by immunohistochemistry and being negative for HER2 expression. A tissue micro array (TMA) was constructed from the asservated surgical specimen according to Kündig *et al*. as described previously (9, 10). TNBC subtyping into Basel-like (BL), Immunomodulatory (IM), Mesenchymal-like (ML), and Luminal androgen receptor (LAR) was performed using a panel of antibodies according to Lehmann *et al*. and Turner *et al*. (3, 5).

For the descriptive analysis, mean (and standard deviation) or median were used for continuous variables and number and percentage were used for categorical variables. To enhance interpretation, stacked bar plots were used to visualize some categorical variables. Chi square and Fisher's exact test were used to test for differences in proportions across subtypes. Overall survival and disease-free survival were visualized with Kaplan–Meier plots of survival probability. All analyses were performed in the R programming language.

The study was approved by the local ethics committee of Zurich, Switzerland (BASEC-No. 2017-00219), according to the national and international ethics guidelines. Informed consent was obtained from all individual participants included in the study.

Results

We collected data from a total of 166 patients with TNBC. For the present study, 31 patients had to be excluded due to the low quality of digital stored images that did not allow a re-evaluation. The average age of the patients was 58 years (sd=14) and was similar across the subtypes (Table I). A higher percentage of postmenopausal women was found in the LAR subtype. Most patients reported a self-detected palpable tumor as the reason for first consultation, followed

Table II. *Imaging characteristics in ultrasound and mammogram of distinct TNBC subtypes according to BI-RADS classification.*

n	Overall 135	BL 49	IM 19	ML 30	LAR 37	*p*-Value
Sonographic shape (%)						0.26
Round/oval	6 (4.4)	1 (2.0)	2 (10.0)	1 (3.3)	2 (5.4)	
Irregular	125 (92.6)	48 (98.0)	17 (10.5)	27 (90.0)	33 (89.2)	
No detected tumor	4 (3.0)	0	0	2 (6.7)	2 (5.4)	
Sonographic margin (%)						0.11
Circumscribed	11 (8.1)	3 (6.1)	3 (15.8)	1 (3.3)	4 (10.8)	
Spiculated	71 (52.6)	30 (61.2)	13 (68.4)	14 (46.7)	14 (37.6)	
Lobulated	49 (36.3)	16 (32.7)	3 (15.8)	13 (43.3)	17 (45.9)	
No detected tumor	4 (3.0)	0	0	3 (6.7)	2 (5.4)	
Sonographic pattern (%)						0.44
Complex	21 (15.6)	9 (18.4)	5 (26.3)	2 (6.7)	5 (13.5)	
Hypoechoic	109 (80.7)	39 (79.6)	14 (73.7)	26 (86.7)	30 (81.1)	
Isoechoic	1 (0.7)	1 (2.0)	0	0	0	
No detected tumor	4 (3.0)	0	0	2 (6.7)	2 (5.4)	
Sonographic posterior pattern (%)						0.031
Posterior enhancement	67 (49.6)	28 (57.1)	11 (57.9)	17 (56.1)	11 (29.7)	
Posterior shadowing	34 (25.2)	13 (26.5)	1 (5.3)	7 (23.3)	13 (35.1)	
No change	30 (22.2)	8 (16.3)	7 (36.8)	4 (13.3)	11 (29.7)	
No detected tumor	4 (3.0)	0	0	2 (6.7)	2 (5.4)	
Sonographic orientation						0.98
Horizontal	90 (66.7)	35 (71.4)	13 (68.4)	18 (60.0)	24 (64.9)	
Vertical	30 (22.2)	10 (20.4)	4 (21.1)	7 (23.3)	9 (24.3)	
Round	11 (8.1)	4 (8.2)	2 (10.5)	3 (10.0)	2 (5.4)	
No detected tumor	4 (3.0)	0	0	2 (6.7)	2 (5.4)	
Mammographic shape						0.007
Focal asymmetry	12 (8.9)	4 (8.2)	1 (5.3)	4 (13.3)	3 (8.1)	
Mass	79 (58.5)	35 (71.4)	11 (57.9)	15 (50.0)	18 (48.6)	
Mass with calcification	18 (13.3)	3 (6.1)	1 (5.3)	3 (10.0)	11 (29.7)	
Calcification only	7 (5.2)	0	0	4 (13.3)	3 (8.1)	
Distortion	0	0	0	0	0	
No detected tumor	19 (14.1)	7 (14.3)	6 (31.6)	4 (13.3)	2 (5.4)	
Mammographic margins						0.077
Circumscribed	51 (37.8)	21 (42.9)	7 (36.8)	11 (36.7)	12 (32.4)	
Spiculated	12 (8.9)	2 (4.1)	0	1 (3.3)	9 (24.3)	
Indistinct	46 (34.1)	19 (38.8)	6 (31.6)	10 (33.3)	11 (29.7)	
Not applicable (no detected tumor/calcification only)	26 (19.3)	7 (14.3)	6 (31.6)	8 (26.7)	5 (13.5)	

by findings from a referring physician and findings during screening at the Breast Center (Table I). Tumor stage did not vary across subtypes. LAR tumors appeared slightly more often well differentiated than other subtypes (29.7%; n=11).

Breast density did not significantly differ within the subtypes. No tumor was seen upon ultrasound in four patients (3.0%), while mammography failed to detect 19 cases of TNBC (14.1%). Benign sonographic classification was given in 19 cases (14.5%). Most of these showed a horizontal orientation, hypoechoic pattern, and posterior enhancement (Table II, Figures 1 and 2). Overall, 66.7% of tumors displayed a horizontal orientation, 22.2% a vertical orientation, and only 8.1% were round, with little variation across the subtypes. In mammogram, 35 (26.7%) cases were classified as benign, mostly due to circumscribed mass without calcification (11.5%) (Table II and Figure 3). Table II shows the univariate associations between imaging features and TNBC subtypes. In ultrasound, BL and IM subtypes were more often spiculated (61.2% and 68.4%) than ML and LAR (46.7% and 37.8%). However, the differences were not found to be statistically significant. Around 80% of tumors exhibited hypoechoic pattern. A possible relationship between sonographic posterior pattern and subtype was observed, with less posterior enhancement in LAR (29.7% *versus* 56.7-57.9%).

BL-TNBC presented more often as a mass without calcification in mammogram than other subtypes (71.4% *versus* 48.6-57.9%). Mammographic margins of LAR-TNBC were more often spiculated (24.3% *versus* 0-4.1% in other subtypes).

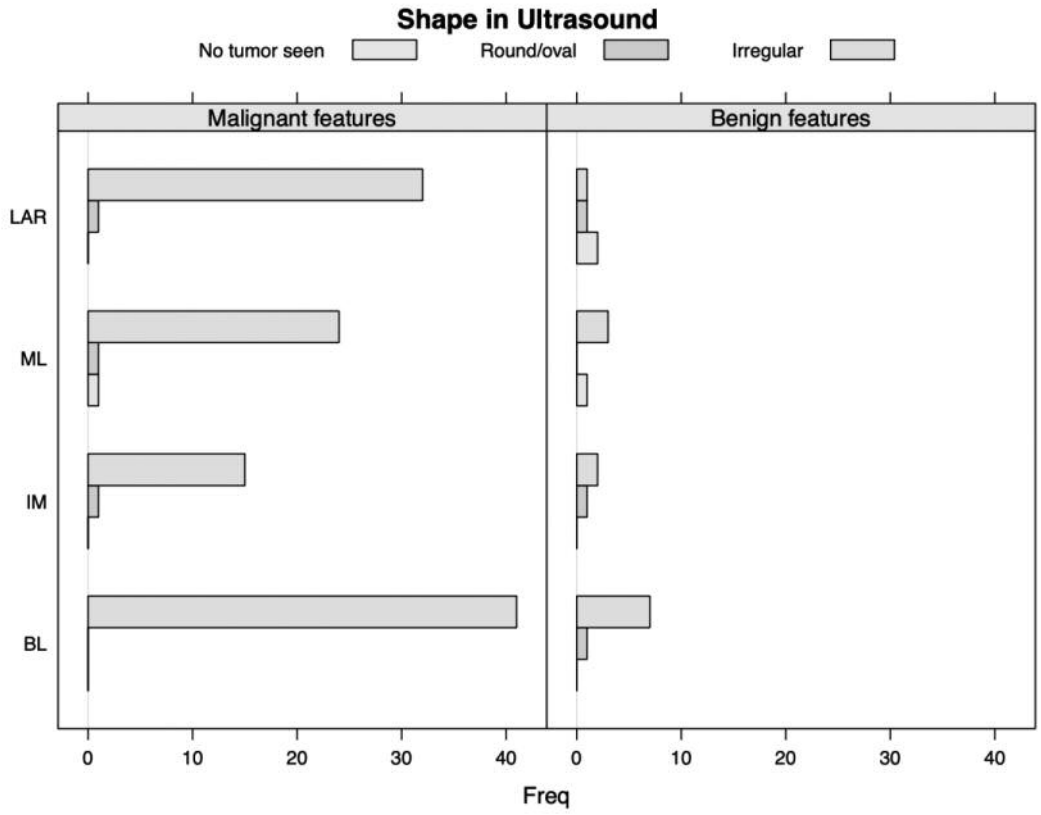

Figure 1. *The relationship of tumor shape in ultrasound to initial BI-RADS classification (benign/probably benign versus probably malignant).*

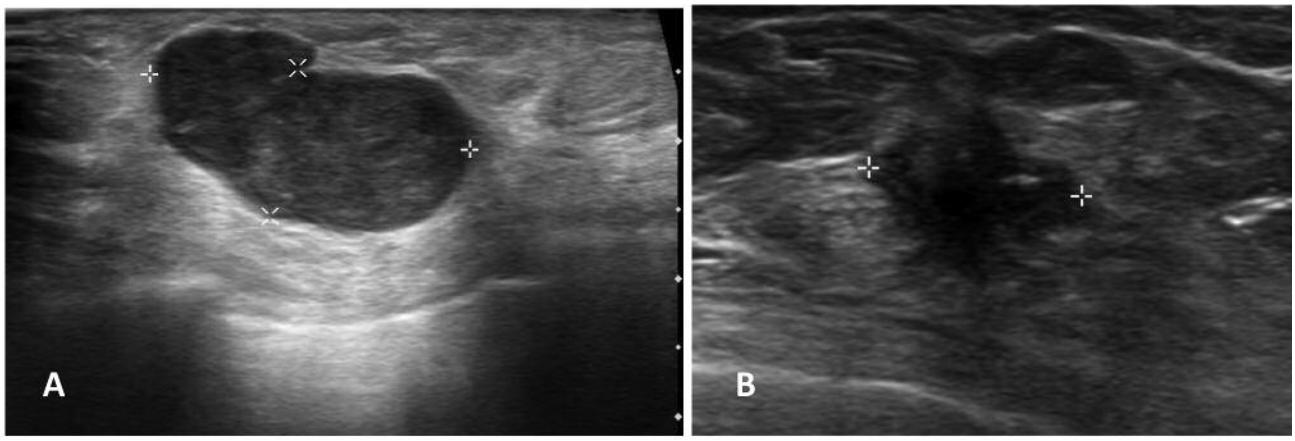

Figure 2. *Ultrasound images of BL-TNBC with lobulated margins (A) and IM-TNBC with spiculated margins (B).*

The relationship of ultrasound and mammogram findings to initial BI-RADS classification (benign/probably benign *versus* probably malignant) is displayed in Figures 1 and 4. In few cases, BI-RADS classification 1 to 3 was given despite "typical" malignant patterns such as mass with calcification in mammogram or irregular shape in ultrasound.

Discussion

Due to the molecular heterogeneity of TNBC, a marker-expression based subclassification has been established over the last few years. Several recent studies have detected different oncogenic alterations and underline the fact that

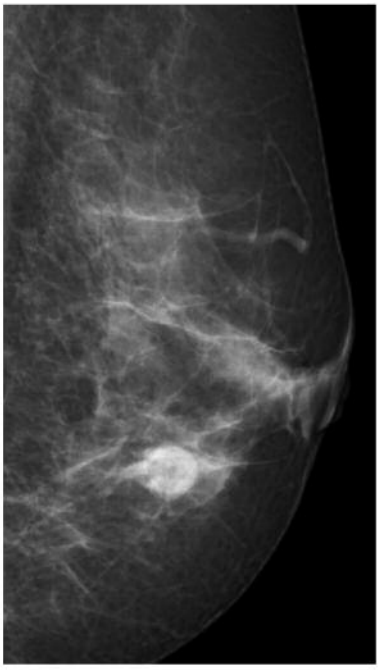

Figure 3. *Mammogram of ML-TNBC with round shape and circumscribed margin.*

TNBC can be further stratified which may lead to a targeted therapy in TNBC (11). Currently, standard treatment for TNBC includes chemotherapy. In many cases, neoadjuvant chemotherapy has the advantages of observing the responsiveness in-vivo, minimizing the surgical procedure, and providing an early start to the systemic therapy. As drug responsiveness differs within the TNBC subtypes, early subclassification in the neoadjuvant setting can be helpful in therapeutic decisions (12, 13). Not only pathological characteristics from a diagnostic biopsy specimen, but also characteristics such as growth pattern in clinical imaging of TNBC subtypes will play an important role in identifying the most promising therapy for every patient.

TNBC is known to present a benign appearance more often in mammogram and ultrasound than non-TNBC (7, 14). Due to the heterogeneous pattern of TNBC especially in ultrasound, some authors have concluded that the predictive value of sonographic appearance might be low when comparing TNBC *versus* non-TNBC (7). However, the histological subtype heterogeneity of TNBC that may explain a broad variety of clinical imaging characters has rarely been considered so far (15, 16). In our study, we compared four histological subtypes of TNBC: BL, IM, ML, and LAR. This subtype classification is more and more used in the current literature; however, data about clinical relevance is still poor (3, 5, 17). Our study is the first that compares the radiological features of four TNBC subtypes.

We observed more often suspicious signs such as spiculated margins or a mass with calcifications in mammogram of LAR subtype. These results are in line with recent studies (18, 19). In these studies, histologic grade did not differ between LAR-TNBC and control group, whereas we observed a lower percentage of poorly differentiated tumors in our group of LAR-TNBC. Lower histological grading and slower growth can be associated with a more spiculated, infiltrating growth pattern, giving the surrounding tissue time for stromal interactions (7). This may explain our mammographic findings; however, they seem to be contradictory to the more frequent lobular sonographic patterns of LAR in our study. In these cases, it is possible that the tumor was overseen in mammogram or showed indistinct margins in the correlating mammogram. Smooth, pushing borders in clinical imaging as well as in the correlating histopathological microscopic pictures are typical for highly aggressive tumors (Figure 5). However, our results imply that not only the grade of differentiation, but also the histopathological subtype of TNBC has an impact on its presentation in ultrasound and mammogram.

BI-RADS classification provides an established algorithm to distinguish benign and potential malignant lesions in the breast. However, daily practice shows a more complex interaction of clinical presentation, risk factors, correlation between mammogram and ultrasound, and individual examiner's pattern recognition. This may explain some initial misclassifications by the first examiner of patients in our study group despite retrospective review of the images occasionally revealing suspicious signs as shown in Figures 1 and 4.

Our study has some limitations to discuss. It is a retrospective single centre study, and despite the reviewers of the clinical images being blinded for the histopathological TNBC subtype, they knew the diagnosis of malignancy. On the other hand, a review process has the advantage of providing a more objective evaluation of imaging features. Furthermore, it allows an interpretation of image characteristics leading to potential misclassification of malignant tumors.

The heterogeneous group of TNBC also shows a great variety of clinical imaging appearance. The authors believe that the presented analysis, as well as further studies, will help to provide an early clinical-pathological subtyping of TNBC prior to a systemic therapy. This is even more relevant, as developing targeted therapies for TNBC subtypes is the topic of latest and ongoing clinical trials (20). For example, if a newly diagnosed TNBC showed spiculated sonographic margins and mass with calcification in the mammogram, histopathological subtyping could be indicated to identify LAR. LAR has a lower pathologic complete response (pCR) to chemotherapy, which might influence therapeutic decisions.

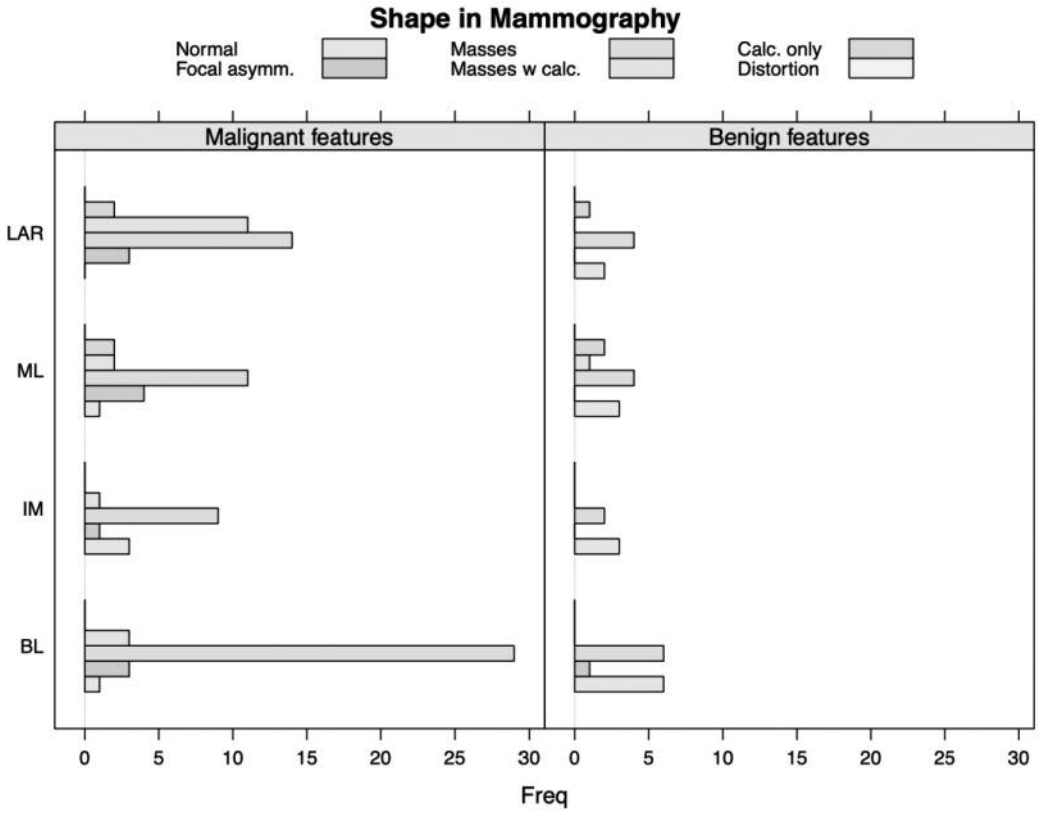

Figure 4. *The relationship of tumor shape in mammogram to initial BI-RADS classification (benign/probably benign versus probably malignant).*

Further studies with higher numbers of subtyped TNBC are warranted to elaborate the impact of histopathological subtype and tumor differentiation on radiological imaging.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

Authors' Contributions

All Authors made substantial contributions to the study, they have approved the current version and agreed on publication.

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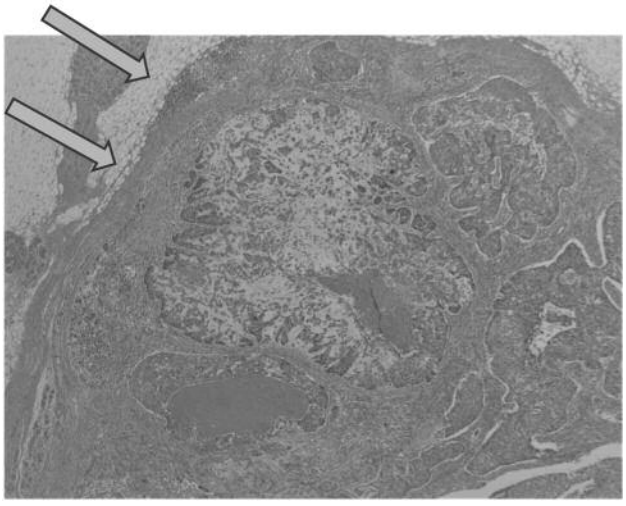

Figure 5. *Microscopic slide (H&E stain) of a surgical specimen of BL-TNBC that presented benign characteristics in ultrasound. Arrows show the smooth, "pushing" border of the tumor.*

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