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Diagnostic Accuracy of Ultrasound Findings in Suspected Breast Cancer Patients: A Tertiary Hospital's Experience

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Abstract **Aim**: This study was aimed at assessing the diagnostic accuracy of ultrasound (US) in patients suspected of having breast cancer and confronting diagnosis by US imaging with histopathological diagnosis in patients of different ages. **Methods:** We performed a prospective case series of 280 patients suspected of having breast cancer, and referred to the tertiary University Hospital of Tirana ("Mother Teresa") for further evaluation, during January 2021-December 2021. These patients were diagnosed with US imaging, using the Breast Imaging Reporting and Data System (BI-RADS) as a tool for evaluating cancer risk. Subsequently, histopathology was carried out (used as a gold standard for diagnosis). The accuracy of US was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV); the performance of US was evaluated by Receiver Operator Curve (ROC), and different associations between variables were assessed by conducting a chi-square test and binary logistic regression. **Results:** With increased age, BI-RADS 2 or 3 cases decreased [48.1% (15-40 years) vs 35.6% (40-49 years) vs 21.4% (50-59 years) vs 9.2% (60-69 years) vs 6.3% (over 70 years)], ($p<0.001$), while BI-RADS 4 or 5 increased (51.9% vs 64.5% vs 78.6% vs 80.8% vs 93.8%), ($p<0.001$), respectively in the above-mentioned age groups. Similarly, with increased age, benign diagnosed cases in histopathology decreased (72.2% vs 57.6% vs 44.3% vs 43.1% vs 21.9%), ($p<0.001$). There was an increase in malignancies according to histopathology amongst older patients, (27.8% vs 42.4% vs 55.7% vs 56.9% vs 78.1%, ($p<0.001$), respectively. In terms of US cancer diagnosis accuracy, our findings showed high sensitivity and NPV (97.9%, 95.7%), not very high specificity (48.2%), and satisfactory PPV and accuracy (65.7%, 73.2%). Meanwhile, the ROC curve showed an Area under the Curve value of 0.81, $p<0.01$. **Conclusion:** The US, using BI-RADS, is a good tool for detecting malignant breast cancer in patients of all ages. The accuracy of US is satisfactory for tertiary diagnostic service, nonetheless, all components must be considered to ensure that the US diagnosis always coincides with the histopathological diagnosis of malignant breast cancer.

Keywords Ultrasound, Breast Cancer, BI-RADS, Albania

1. Introduction

Since the end of 2020, breast cancer has had the highest prevalence among cancers, leading to almost 685,000 deaths worldwide [1]. Various data shows a growing tendency in the incidence of breast cancer in Albania, with a rate of about 32.9% in 2020 [2]. The population of Albania is 2877800 based on Worldometer elaboration of the latest United Nations data [3]. This reinforces the need for timely diagnosis, both in healthy population screening programs as well as in suspected breast cancer cases. The role of ultrasound (US) in the diagnosis of breast cancer is crucial, particularly in dense breasts which have been insufficiently evaluated by mammography [4]. Continuous improvement in US and user performance makes it possible to differentiate solid masses as benign or malignant [5]. The American College of Radiology developed the Breast Imaging-Reporting and Data System (BI-RADS) as a risk assessment tool, which contains an accepted lexicon, even for the US, to describe mammary imaging results [6]. BI-RADS was found to be reliable in the detection of malignant breast lesions [7]. On the other hand, the gold standard for diagnosing breast cancer is histopathology [8]. The role of histopathology is very important, not only in differentiating between benign and malignant tumors but also in the treatment plan and prognosis of the disease [9]. Decision-making in breast surgery is complex, which is why the accuracy of the diagnostic instrument is important [10]. Sub-group differences among populations may affect the instrument diagnosis accuracy, given that breast cancer has given a discrepancy for factors such as insurance status, race and socio-economic status. [11-12]. It is therefore necessary to carry out such studies in different settings and facilities. Albania has paved the way for a national breast cancer screening program in primary care based on clinical examination and mammography screening [13]. However, the awareness of the Albanian population of breast cancer is not at the highest level and the number of mammography examinations is even lower than the potential of performing these examinations [14]. Against this background, the diagnosis of breast cancer has shifted from clinical detection of palpable masses by primary and secondary healthcare providers to US diagnosis at the only tertiary oncology service of the University Hospital of Tirana: “Mother Teresa” in Albania. For all of the above, it is important to examine the validity of breast cancer diagnosis through US imaging in presumed cases of breast cancer.

2. Methods

A prospective case series study was conducted during January 2021-December 2021. 280 patients underwent a US diagnostic test followed by a breast biopsy, which was histopathologically assessed. These patients originated from the referral system (primary and secondary healthcare) as patients with palpable breast mass. All these patients were referred by specialist physicians to the University Hospital Center: "Mother Teresa", Oncology Service, as part of the tertiary healthcare service in Albania. After consultation with tertiary specialist surgeons, they were referred for US radiological examination and evaluation by specialized radiologists in breast imaging.

The instrument used for the imaging diagnosis was the Chison US, with a 10 MH linear transducer.

Two radiologists conducted radiographic examinations independently, then they agreed on the tumor BI-RADS classification. Next, patients underwent a TRU-CUT 14 g needle biopsy. Histopathology confirmed by a single pathologist was the reference standard for evaluating the criterion validity of the US test. The data collection was performed by one of the radiologists, who collected the US diagnostic and histopathological diagnostic data.

BI-RADS was considered to convey the radiological characteristics of the mammary masses in quantitative measurement terms. Then, the BI-RADS 0-5 classification was used to dichotomize the US-diagnosed tumors into "benign" and "malignant". Depending on the type of cancer, histopathology-diagnosed tumors were also dichotomized into "benign" and "malignant" tumors. Age of patients was categorized into 5 categories (in years): “15-40”, “40-49”, “50-59”, “60-69” and “over 70”. The size of the tumor, based on US imaging diagnosis findings was categorized into: “1-10 mm”, 10-20 mm, and >20 mm, while malignant tumors were diagnosed histopathologically according to grades. Given that grades 0 and 4, according to TNM Grading System [15] were missing among these patients, this variable was dichotomized into: “grades 2” and “grade” 3.

The respective percentages were calculated to describe the category variables, while for continuous variables, the mean and standard deviation were calculated. Chi-square was used to examine the differences between categorical variables. Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) and Accuracy (measurement) were calculated to describe the accuracy of US test. Binary logistic regression was used to assess the association of BI-RADS diagnostic classification and tumor size detected by the US with histopathology’s diagnosis. Receiver Operator Curve (ROC) was used to illustrate the performance of the US diagnostic test. A p-value of <0.05 was considered statistically significant. Statistical analysis was conducted using Statistical Package for Social Sciences, statistical software, version 25.0.

All the participants gave their oral consent for the anonymous use of their data for research purposes. In terms of ethical considerations, this study was conducted according to the Helsinki Declaration protocol.

3. Results

The mean age ($\pm$ standard deviation) of 280 participants was 55.9 ± 14.9. With increased age, BI-RADS 2 or 3 cases

decreased [48.1% (15-40 years) vs 35.6% (40-49 years) vs 21.4% (50-59 years) vs 9.2% (60-69 years) vs 6.3% (over 70 years)], (p<0.001), while BI-RADS 4 or 5 increased (51.9% vs 64.5% vs 78.6% vs 80.8% vs 93.8%), (p<0.001), respectively in the above-mentioned age groups. Similarly, with increased age, benign diagnosed cases in histopathology decreased (72.2% vs 57.6% vs 44.3% vs 43.1% vs 21.9%), (p<0.001). There was an increase in malignancies according to histopathology amongst older women, (27.8% vs 42.4% vs 55.7% vs 56.9% vs 78.1%, (p<0.001), respectively. There were no significant differences between increasing age and increasing tumor size on US findings (p=0.7) or increasing age and differentiation of malignant grade in histopathological diagnosis (p=0.7). Of note, there were no cases diagnosed with BIRADS 0 and 1 (Table 1).

Table 2 shows that the sensitivity values of the diagnostic US test (BI-RADS) are 100 percent for tumors with small sizes 1-10mm compared to 97.2%, respectively in the two other categories of larger tumors of 10-20 mm, and over 20 mm. The same trend exists for other measurements of test accuracy, with higher values in 1-10mm size tumors vs 10-20 mm size tumors, or over 20 mm tumors, as regards specificity (50% vs 47.4% vs 48.4%), PPV (80% vs 63.6% vs 68.3%), NPV (100% vs 94.7%, 93.8%) and accuracy (83.3% vs 71.6% vs 74.4%). In terms of US cancer diagnosis accuracy, our findings showed high sensitivity and NPV (97.9%, 95.7%), not very high specificity (48.2%), and satisfactory PPV and accuracy (65.7%, 73.2%). (Table 2) The ROC for BI-RADS US diagnosis was shown in Figure.1, with AUC value 0.809, p<0.01. An AUC of 0.8 to 0.9 is considered excellent [16] (Figure 1).

Table 1. Distribution of BI-RADS, US diagnosis findings, histopathological diagnosis findings, US tumor size, and malignancy grades, by different age groups

Variables	N	Age categories in years (Respective percentages)					P value
		15-40 (%)	40-49 (%)	50-59 (%)	60-69 (%)	>70 (%)	
US (BI-RADS):							
BI-RADS 2-3	280	48.1	35.6	21.4	9.2	6.3	<0.001
BI-RADS 4-5		51.9	64.5	78.6	90.8	93.8	
Histopathology:							
Benign	280	72.2	57.6	44.3	43.1	21.9	<0.001
Malignant		27.8	42.4	55.7	56.9	78.1	
Tumor size:							
1-10 mm	213	2.4	0.0	3.5	2.0	8.7	0.7
10-20 mm		31.0	35.7	36.8	38.8	26.1	
>20 mm		66.7	54.3	59.6	59.2	65.2	
Histological grade (malignancy):							
Grade 2	127	58.3	62.5	75.0	72.7	72.7	0.7
Grade 3		41.7	37.5	25.0	27.3	27.3	

Table 2. The diagnostic accuracy of US (BI-RADS) compared to gold standard (histopathology)

	N	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV† (%)	Accuracy (%)
1-10 mm	213	100.0	50.0	80.0	100	83.3
10-20 mm	213	97.2	47.4	63.6	94.7	71.6
> 20 mm	213	97.2	48.4	68.3	93.8	74.4
All	280	97.9	48.2	65.7	95.7	73.2

*Positive Predictive Value, †Negative Predictive Value

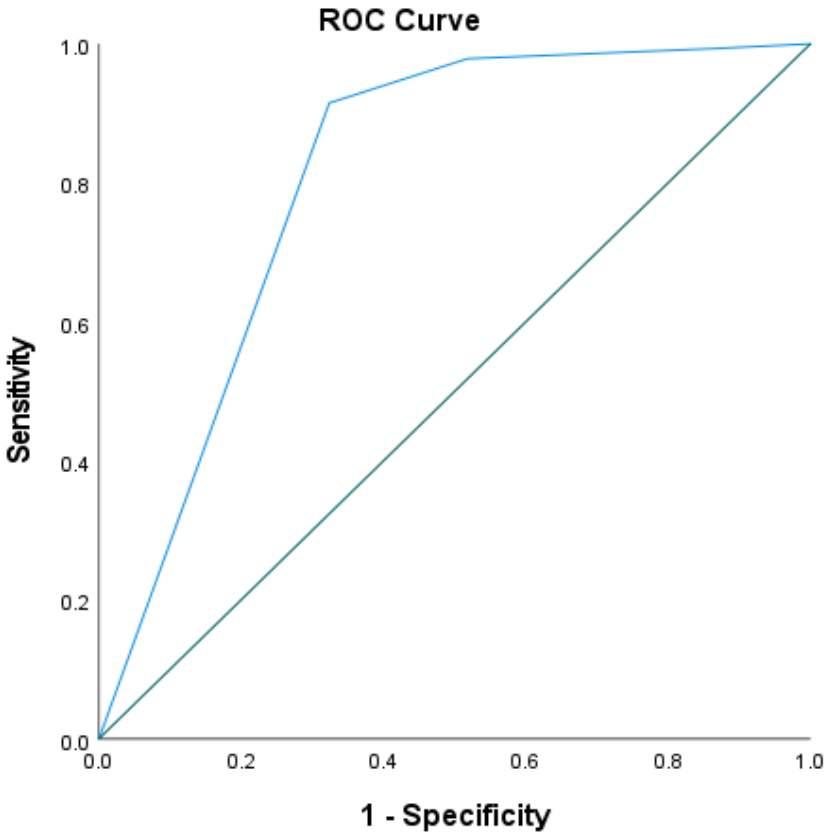

Figure 1. US BI-RADS ROC curve

The results of the binary logistic regression show increasing one unit of BI-RADS is associated with a 7 times increase in the odds of malignant histopathology diagnosis (95% confidence interval: 4.2–11.6). Tumor size was not associated with malignant histopathology (OR = 1.0) (Table 3).

Table 3. Crude (unadjusted) logistic regression model of the association between BI-RADS classification and tumor size (US findings) with final histopathological diagnosis of tumors

	S.E.*	Wald**	df†	P Value	OR***	95% CI††
BI-RADS	.258	56.982	1	<.001	7.0	4.2-11.6
Tumor size	0.02	0.078	1	0.78	1.0	0.98-1.02

**SE* standard error, ***Wald* test is used to compare models on best-fit criteria, †*df* degree of freedom, ****OR* odds ratio, ††*95% CI* 95% confidence interval

4. Discussion

Clinical, mammographic and US diagnostics are very important and complementary in perioperative breast cancer diagnostic attempts. The diagnostic performance of the US in detecting breast cancer has already been demonstrated, providing satisfactory percentages of sensitivity and specificity [11]. Moreover, US diagnosis offers advantages in cost-effectiveness, non-invasive application and good acceptance by patients, as a radiation-free instrument [17]. Given that many countries have limited resources for the diagnosis of breast cancer, it is very important that clinical, imaging and pathological correlation be persistent [18]. Although in Albania, palpable clinical breast examination by PHC providers and the mammography screening program have been sufficiently promoted, the Albanian population appears to be stigmatized and little aware of breast health [19]. Therefore, the first presentation for the evaluation of breast health is the presence of a palpable mass, which was also a criterion for the inclusion of the population in the study. In the context of the above, for countries such as Albania, breast US diagnosis and its accuracy in differentiating these breast tumors is particularly important.

The findings of our study showed a significant increase in malignant breast cancer diagnosis with age, both in imaging and histopathology. Scientific evidence from numerous studies indicates that about 1/3 of diagnosed breast cancer patients are more than 70 years old, underlining age as a risk factor for breast cancer and probably the delay in rapidly diagnosing this disease [20]. In a similar study in India, the BI-RADS score tended to show a more benign condition in women under 40 years [21]. Another clinical study found that the diagnostic criterion for the US that differentiates between benign and

malignant cancers is influenced by the age and size of the tumor [22]. However, in this study, increasing the size of the tumor detected by US imaging does not increase the likelihood of a malignant histopathological diagnosis (OR = 1.0). There are also no significant differences in age with respect to tumor size or histopathological grade.

As for the accuracy of the US in breast cancer detection, in a meta-analysis conducted, the evidence showed that the US has a sensitivity of 80.1% and a specificity of 88.4% [11]. Our study showed the values of sensitivity, specificity, PPV, NPV and accuracy, respectively, 97.9%, 48.2%, 65.7%, 95.7% and 73.2%. Even though the meta-analysis data showed lower sensitivity and higher specificity in low- and middle-income countries [11], in our study in Albania, as a middle-income country, there was evidence of high diagnostic US sensitivity, along with lower US specificity. In a similar study, in a country with similar demographic features, such as Kosovo, with diagnostic purposes, the US sensitivity value is lower, whereas the US specificity value is higher, at 72.6% and 88.5%, respectively [23]. Our study found that all magnitudes of diagnostic accuracy in the US are slightly higher in small tumors 1-10 mm compared to tumors larger than 10 mm. However, a Chinese study identified lower sensitivity of US in tumors smaller than 1 cm in size, compared to those of 1cm-2cm [24]. Thus, our study showed high values of sensitivity, NPV and accuracy, but not very high specificity and PPV of the US. In addition to these values, our Area under the Curve (AUC) results compared to a similar study conducted in the USA were satisfactory (AUC values: 0.809, $p < 0.01$ versus 0.783-0.848) [25]. Results from logistic regression showed that a one-unit increase in the BI-RADS score led to a 7 times more likelihood of being diagnosed as malignant cancer on histopathology. Consistent with the literature [26], moderate specificity and PPV values suggest that some patients not affected by breast cancer may have been positively diagnosed. These values could be explained by inherent limitations of the ultrasound and overlapping features of some benign tumors that can produce false-positive cases. In all cases, patients must confirm the diagnosis through histopathology. It has been shown that overdiagnosis results in excessive treatment which, in the case of breast cancer, can result in unnecessary surgery, unnecessary costs and post-surgery complications [27].

It is known that diagnostic instruments have different objectives and different eligibility criteria for target-inclusive populations, contrary to screening instruments [28]. In our study, comparisons were made with similar non-screening, diagnostic studies. Though, our study assesses the diagnostic accuracy of ultrasound in breast cancer, it also provides an indicator of re-objectification towards the US breast cancer screening approach. In countries such as Albania, with some of the aforementioned problems, the results of the diagnosis of breast cancer at the tertiary level serve to better identify and improve the specifics of the diagnosis, such as the age of the patients, the referral system, the diagnostic capacity of the doctors, and the timely intervention.

The study has some limitations. The two radiologists, as part of the study, agreed on the BI-RADS classification, but no agreement coefficient was calculated for the measurement of inter- or intra-reader variability. Due to the referral of suspected cancer patients with palpable mass to a tertiary university hospital, the study may have been affected by framing bias, in which radiologists made the decision from the information presented, rather than the facts of diagnostic imaging, per se.

In terms of histopathological diagnosis, tumors were evaluated only by one anatomo-pathologist, without having at least another control anatomic-pathologist. Since numerous studies show that BI-RADS 3 may have a malignancy rate of 2% [29], the conversion of the multinomial variable BI-RADS into a dichotomous variable or its use as an ordinary variable may have an impact on the study results. Case series cannot avoid selection bias, nor does it permit generalization of results for all breast cancer suspected patients.

5. Conclusions

The US, using BI-RADS, is a good tool for classifying and reporting breast imaging results. With age, the chances of detecting breast cancer in the US increase for patients who have already demonstrated palpable mass. The accuracy of US is satisfactory for tertiary diagnostic service, nonetheless, all components must be considered to ensure that the US diagnosis always coincides with the histopathological diagnosis of malignant breast cancer.

Conflict of Interest Statement

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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