**BIRADS 3 and 4 lesions viewed by ultrasound and not seen in digital mammograms and tomosynthesis.**

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**Abstract**

**OBJECTIVE:** analyze the usefulness of ultrasound in detection of breast cancer, at a mammary gland imaging center, focusing primarily on nodules not seen in digital mammograms and tomosynthesis, in a prospective study of 1,600 mammograms for screening.

**INTRODUCTION:** the mammogram, in its analogic or digital mode, is well known as an effective imaging method for early detection of breast cancer and the only screening method which proven to reduce mortality from breast cancer; however, superimposition of mammary tissue, added to its high density, are obstacles to interpreting and detecting lesions even when using digital mammogram by tomosynthesis, for which reason complementary use of ultrasound is imperative to detect lesions.

**MATERIAL AND METHODS:** 1,600 asymptomatic patients who took part in a screening study to detect mammary gland cancer, in an age range of 40 to 65 years, were included. All of them underwent digital mammogram, tomosynthesis, and ultrasound, including in this report only those in whom BIRADS category 3 and 4 nodules detected by ultrasound were confirmed, without representation or not seen in digital mammograms or tomosynthesis. All the studies were evaluated by 5 radiologists with sub-specialization in mammary imaging.

**RESULTS:** of 1,600 patients, BIRADS category 3 and 4 nodules were confirmed in 270, 52 of them detected only by ultrasound and not seen by digital mammogram or tomosynthesis.

**CONCLUSION:** in a dense breast there are greater probabilities of overlooking calcifications, asymmetries, or nodules in digital mammogram or tomosynthesis, which underscores the importance of adding ultrasound to mammogram screening.

**KEYWORDS:** breast cancer; nodules; mammogram; tomosynthesis; mammary ultrasound

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Received: January 22, 2016
Accepted: July 12, 2016

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**This article must be quoted as**
INTRODUCTION

Analogue or digital mammography is considered an effective imaging method for early detection of breast cancer and the only screening method that has proven to reduce breast cancer mortality; however, overlapping breast tissue and high density breasts have made interpretation and detection of lesions difficult. As a recent tool, digital tomosynthesis, as a tomographic modification of digital mammography, adds one more plane to the traditional view, thereby it is referred to as 3D mammography, helping in many cases to reduce or eliminate overlapping in the breast tissue. Images are processed in conventional views, using an algorithm that is similar to the one used in computed tomography. However, even with digital tomosynthesis, the examination of dense breasts to find lesions is still very difficult, especially in case of lesions not surrounded by fat tissue.

Breast ultrasound, which was introduced since the seventies in the last century, was initially indicated to differentiate cysts and solid nodules or palpable tumors, and was established as a complementary method after mammography. Since the eighties, it was also considered to be capable of creating a detailed map of breast structure anatomy and to establish the diagnosis of benign or malignant lesions by itself.

Currently, the use of breast ultrasound is not limited to the differentiation between solid or cystic lesions, but it also provides additional morphology details to the anatomical structure of the breast as well as to the findings in the study, particularly to each lesion, such as solid nodules; it also has additional tools such as color Doppler, to see the vascularization, as well as elastography, revealing the hardness or stiffness of the lesion to better distinguish between benign and malignant lesions. It is the first method of choice for breast examination in young women having a palpable tumor.

Breast ultrasound, combined with clinical examination and mammography, significantly increases sensitivity and specificity of breast exams, especially for dense breasts, that is, breasts with radiopaque stromal and epithelial tissue compared to radiolucent fat elements seen in mammography.

Breast ultrasound involves a careful analysis and its effectiveness depends as much on the quality of the equipment as well as the operator, and the ultrasound technician needs to be highly specialized, since the detection of lesions totally depends on his or her perception, resulting in high inter-observer variability. The absence of an image or overall breast tissue pattern makes this method less reproducible. These factors limit the use of ultrasound in some countries, where specialized radiology work is very costly.

In malignant palpable tumors, breast ultrasound has 99-100% sensitivity, even with negative mammography. When there is a palpable tumor with negative targeted ultrasound, there is a very low likelihood of finding a cancer. Also, ultrasound is the method of choice to guide percutaneous interventional procedures, such as preoperative marking, fine needle aspiration, core needle biopsy or aspiration biopsy. In select cases ultrasound allows to locate and take a biopsy of microcalcifications clearly identified in mammography.

Indications for breast ultrasound:

- Clinical disturbances with or without mammography findings
- Mammography findings: complement
- Complementary study of dense breasts
- Examination of young, pregnant, or breast-feeding patients
• Examination of male breasts
• Nipple secretion study
• Follow-up of benign lesions
• Examination of breasts with implants
• Interventional procedures
• “Second look” after MRI

Ultrasound in asymptomatic patient screening

The recommendation of the American College of Radiology is to classify breasts in 4 categories according to the radiological density of the parenchyma. The BIRADS classification uses the lexicon heterogeneously dense breasts and extremely dense breasts, which could obscure small masses, and decrease sensitivity, and it is well established that sensitivity in mammography decreases as density increases.\(^5\)

The relative cancer risk in women with heterogeneously dense breasts, compared to average women is approximately 1:2, and the relative cancer risk in women with extremely dense breasts, compared to average women is 2:1;\(^9\) also, there is an important risk of not finding a small cancer in a dense area in mammography, even with double reading or with digital mammography. On the other hand, there are “blind” areas in mammography, such as the inframmary sulcus and the lower inner quadrant, which could be outside the area covered in the examination.

False negative results in mammography account for 10 to 30% of studies, mainly because small nodules are not detected.\(^9\) Solid nodules are considered as probably benign, BIRADS 3 in ultrasound when they have no suspicious findings and have 1 to 3 benign criteria, described by Stavros (circumscribed, hyperechoic, ovoid in shape).\(^10\)

On mammography, undetermined or suspicious nodules because of their shape and margins (irregular), are considered BIRADS 4, and are best characterized by ultrasound.\(^11\) Several studies agree that 75% of a cancer “exclusively” detected by ultrasound is under 1 cm.\(^12\)

The systematic use of breast ultrasound not only increases cancer detection, but also benign and undetermined lesions. Buchberger, for example, found 365 benign lesions in his series, 60% were solid nodules and 40% complicated cysts.\(^13\)

OBJECTIVE

Update the evidence on the usefulness of ultrasound in breast cancer detection, at a breast imaging center, focusing on nodules not seen with digital mammography or digital tomosynthesis, mainly in dense breasts, in a prospective study of 1600 patients conducted between February 1\(^{st}\) and May 30, 2015.

MATERIAL AND METHODS

Prospective study that included 1600 asymptomatic patients that came for breast cancer screening. The age range was 40 to 65 years. Patients had a digital mammography, digital tomosynthesis and ultrasound. This study only includes patients with nodules category BIRADS 3 AND 4, found with ultrasound and not depicted or seen in mammography. Cystic nodules were not included (simple or complicated) or known nodules with benign features and behavior (BIRADS 2), patients who were followed because of nodules, patients with referred palpable nodules, patients with breast implants, biopsy or previous surgery, and patients who revealed nodules by digital mammography, digital tomosynthesis or ultrasound.

All patients were examined using digital mammography, digital tomosynthesis with two
machines Selenia-Dimention (Hologic®), in the usual CC and MLO views, with tomosynthesis in CC view, choosing this view because a greater amount of tissue is covered; 1mm sections were used with variable number of sections in each patient, according to the breast thickness. Ultrasound studies were performed using two Philips® IU22 ultrasound machines with 13 and 17 MHz high frequency lineal transducers. All the studies were prospectively evaluated by 5 radiologists who had a breast gland subspecialty, with 5 to 25 years experience in breast examinations.

Ethical considerations

All studies were performed with informed consent of patients and following ethical medical and institutional codes.

RESULTS AND STATISTICAL ANALYSIS

Out of 1600 patients included (with digital mammography, digital tomosynthesis and ultrasound) 270 proved to have BIRADS 3 and 4 nodules; of which 52 were seen only by ultrasound (Table 1), category BIRADS 3 (34 cases) and BIRADS 4 (18 cases) (Table 2). As examples we have: BIRADS 3 nodules in patients with pattern b (American College of Radiology) (Figure 1) and nodules with a dense breast pattern (Figure 2), with 1.8 cm diameter (Figure 3), all of which were not found with mammography or tomosynthesis. The size of the observed nodules had a range of 0.4 to 1.8 cm (Table 3).

Out of the nodules with BIRADS 4 category (16 cases), 10 had a core needle biopsy, 5 resulted to be carcinomas, the smallest was 0.88 mm and the largest was 1.2 cm. Ductal carcinoma was confirmed in 5, 3 in situ and 2 infiltrating. Examples: BIRADS 4A category nodules (Figure 4) and BIRADS 4b, both resulted in infiltrating ductal cancer (Figure 5).

<table>
<thead>
<tr>
<th>BIRADS</th>
<th>Rate</th>
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<tr>
<td>BIRADS 3</td>
<td>31 (34)</td>
</tr>
<tr>
<td>BIRADS 4</td>
<td>69 (18)</td>
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The rest of the suspicious cases are being followed or pending to define treatment. The patients were in a range of 40 to 65 years of age.

Due to world incidence and prevalence and the innumerable technological advances, the number of cases with breast cancer diagnosis has constantly increased. The greater the technological advances, the greater the detection of breast cancer, especially in early stages. More women undergo radiological screening studies each day due to greater information and better access. No one can argue that the use of mammography has reduced mortality from this disease when found at early stages. The introduction of different technologies such as ultrasound has allowed to improve diagnosis, especially in patients in whom screening studies (such as digital mammography and digital tomosynthesis) show a dense glandular pattern and also due to the relative cancer risk (1.2) in women with heterogeneously dense breasts and the relative cancer risk (2.1) in women with extremely dense breasts. There is also an important risk of not finding a small cancer in a dense area in mammography, even with double reading or with digital tomosynthesis. Therefore, the importance of including ultrasound in breast cancer screening, allowing to show lesions (cysts, solid nodules or

Table 1. Total number of patients (270) BIRADS 3 and 4

<table>
<thead>
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<th>Nodules seen on screening mammography</th>
<th>Rate</th>
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<tr>
<td>Digital mammography, digital tomosynthesis and ultrasound</td>
<td>81 (218)</td>
</tr>
<tr>
<td>Only with ultrasound</td>
<td>19 (52)</td>
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Table 2. Nodules seen only with ultrasound (52)
Figure 1. BIRADS 3 nodule (arrow) in patient with pattern b (American College of Radiology).

Figure 2. BIRADS 3 nodule (arrow) in 40-year-old patient with dense glandular pattern.
distortions) that otherwise would be overlooked, perhaps waiting for the next annual study to be revealed or until they become larger in diameter and palpable in case of neoplasms.

This paper focused on the detection of solid, non-palpable nodules, not known from previous studies, as well as on their classification according to their ultrasound characteristics; to emphasize the importance of their timely detection in case they are not suspicious (BIRADS 4) or their short term follow-up (BIRADS 3 category) and evaluate their behavior; all this according to the criteria of the American College of Radiology concerning shape, size, outline, content and Doppler vascular pattern or elastography stiffness.

A dense breast refers to the relation between the fibroglandular tissue and the fat content, which are criteria that have been well defined by several authors and by the American College of Radiology in four categories that go from less density (A) to more density (D) in mammography. The greater the density of fibroglandular tissue (especially made by the glandular epithelium or acinotubular components, ducts, and intra and interlobular stromal component), the greater the likelihood of overlooking calcifications, asym-

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Table 3. Size of nodules

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<tr>
<th>Size</th>
<th>Number of cases</th>
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<tr>
<td>0.1 a 0.5 cm diameter</td>
<td>11</td>
</tr>
<tr>
<td>0.6 a 1.0 cm diameter</td>
<td>29</td>
</tr>
<tr>
<td>More than 1 cm diameter</td>
<td>12</td>
</tr>
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Figure 3. 1.8 cm nodule (arrow), BIRADS 3, not shown on mammography or tomosynthesis, in a dense glandular pattern.
Figure 4. Single nodule (arrow), BIRADS 4A that was reported as infiltrating ductal cancer.

Figure 5. BIRADS 4 nodule (arrow) that was reported as infiltrating ductal cancer.
metry or nodules using digital mammography or
digital tomosynthesis, and thus the importance of
adding ultrasound to screening with mammog-
raphy, especially in C and D density patterns.¹ five

CONCLUSION

Our study revealed 5 ductal carcinomas by ultra-
sound, not detected in digital mammography or
digital tomosynthesis screening, in patients with
dense mammography pattern C and D (American
College of Radiology), thereby the importance of
including ultrasound in screening these types of
mammographic patterns.

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