Purpose

Introduction

Breast cancer is the most common malignancy in women and the most common cause of death due to cancer in women (1).

Mammography is worldwide used as the technique of choice to detect breast cancers. Several trials have demonstrated that mammography can reduce the mortality due to breast cancer up to 30% (2), but some authors do not agree with these results (3). In fact, an important controversy exists regarding the results of the population-based screening campaigns (3). Probably one of the most important factors influencing the results is the breast density. It is well known that the sensitivity of mammography drops in dense breasts (as low as 30%-48%) (4). The main reasons are the overlapping tissue and the low contrast of tumors in comparison with the surrounding parenchyma. Both produce false positive (recall rate) and false negative results.

This low sensitivity has induced the use of additional techniques, such as ultrasound (US) and/or Digital Breast Tomosynthesis (DBT). The former has been proven to have good results in dense breasts (6) but it is an operator dependent and time consuming technique. Due to these reasons, US is not routinely used for screening purpose, although it plays an important role as a problem solving technique.

DBT has been the latest development of digital mammography, acquiring multiple low-dose images of the breast and reconstructing the images in a series of multiple slices, all of them parallel to the detector (7). DBT has been found to increase the detection of breast cancers up to 27% (8).

Purpose

Our purpose was to evaluate the diagnostic accuracy of Digital Mammography (DM) and the combinations of DM with US and the combination of DM with DBT.
Methods and materials

Patients selection

From November 2011 to December 2013, a total number of 9121 women underwent digital mammography at our institution. According to our protocol, additional DBT and US were routinely performed for all patients showing density patterns 2, 3 and 4 according to the American College of Radiology (ACR), as well as for all patients with lesions detected on digital mammography (using DBT and US as problem solving techniques).

An informed consent was given to all patients.

Study design

We conducted a retrospective study, following the recommendations of our Institutional Review Board, selecting an enriched sample of 1042 patients (1041 female and 1 male) who underwent the three imaging techniques: DM+DBT+US.

The selection criteria were: patients with biopsy proven malignancies (84 patients), patients with biopsy proven benign lesions (258 patients) and patients with normal studies or benign conditions, with no biopsy but at least one year follow-up without significant changes (700 patients). The informed consent for this retrospective study was waived.

Both DM and DBT studies were obtained with the Siemens Inspiration unit (Siemens Medical Solutions, Erlangen, Germany). DM was performed using both 45° mediolateral oblique (MLO) and craniocaudal (CC) views. DBT was routinely performed using a single 45° MLO view, but additional CC DBT views were used as problem solving technique when necessary. The wide angle used by DBT (50°) induces a long acquisition time (20 seconds) limiting the routine use of DBT to a single view (usually MLO view). The radiation dose of DM+DBT for each breast was 3.8 mGy for 45 mm PMMA (polimethilmethacrylate) (1.9 mGy for DM two views and 1.9 mGy for one DBT view), well within the accepted limits (5mGy) (9).

The US study was performed using a MyLab 60 unit (Esaote, Genoa, Italy), with a multifrequency (5-13MHz) linear array transducer.

One expert radiologist, with more than 15 years dedicated to breast diagnosis, evaluated retrospectively all the cases.
For each case, the reader evaluated DM, classifying it according to the BI-RADS categories.

Then, with the information of DM, the reader evaluated the additional DBT, and reclassified the case (DM+DBT). This first lecture took about one month. Three weeks later, the same reader reviewed again DM, maintaining the previous categorization, as well as the additional US studies. These US studies were evaluated in conjunction with the DM information (DM+US). Finally, there were three classifications for comparison: the BI-RADS classification of DM alone, the BI-RADS classification of DM in conjunction with DBT and the BI-RADS classification of DM plus US.

The cases classified as BI-RADS categories 3, 4 or 5 were considered as positive, whereas the categories 1 or 2 were considered as negative. The reader was blinded to the final results.

**Statistical Analysis**

All the data were recorded using the SPSS software (20.0 version).

The sensitivity and specificity as well as the statistical significance of both were calculated using the PEPI software (4.04 version).

The Areas under the Curve (AUC) of the different combinations of techniques (DM; DM+DBT; DM+US; DM+DBT+US) were calculated and compared with the SPSS software by using a z test.

Statistical significance was established for p<0.05.
Results

A sample of **1042** patients was selected (mean age: 51.6, range: 22-88). Out of them, 84 patients had histologically proven malignant lesions and 258 patients had benign lesions. The remaining 700 patients had no lesions or benign lesions with no biopsy but no changes during at least one year follow up.

Fig. 1

**References:** Radiology, Clinica Universidad de Navarra, Clinica Universidad de Navarra - Pamplona/ES

The distribution of the malignant cases according to the histology and the detection by the different techniques are shown in this table.
DM detected 69% of malignant tumors, while additional US increased the sensitivity by 23.8%, additional DBT by 17.8% and the combination DBT+US detected 29.76% additional tumors.

The sensitivity and specificity of DM and the different combinations of the three techniques are shown in this slice.
The highest sensitivity was achieved by the combination of the three techniques (DM + US + DBT), reaching 98.81%.

The sensitivity of DM+DBT as well as the sensitivity of DM+US were significantly higher (p<0.05) than the sensitivity of DM.
There were not statistical differences between DM+US and DM+DBT regarding the sensitivity.

**Fig. 4**
**References:** Radiology, Clinica Universidad de Navarra, Clinica Universidad de Navarra - Pamplona/ES
Conversely, the specificity of DM+DBT and DM+US were significantly lower than the specificity of DM (p<0.05).

The specificity of the combination DM+DBT was significantly higher than the one with DM+US (p<0.05).
### Table 3. Specificity of DM and the different combinations

<table>
<thead>
<tr>
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<th>DM</th>
<th>DM + US</th>
<th>P value</th>
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<tbody>
<tr>
<td>SP (%)</td>
<td>88.20</td>
<td>74.32</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

- DM + US and DM + DBT vs DM (p < 0.05)

**Fig. 6**

**References:** Radiology, Clinica Universidad de Navarra, Clinica Universidad de Navarra - Pamplona/ES
The ROC curves and the comparison among the different techniques are shown in this figure.
The addition of US and/or DBT to DM significantly increased the AUC. In the comparison between DM+US vs DM+DBT there were no significant results (p=0.73).

### Cases
Fig. 9: 53 year-old asymptomatic woman. This is an example of an additional breast tumor detected by US: both mammogram and DBT were normal.

References: Radiology, Clinica Universidad de Navarra, Clinica Universidad de Navarra - Pamplona/ES.
**Fig. 10:** 58 year-old asymptomatic woman. This is an example of another tumor detected by additional DBT, the remaining techniques were negative.

**References:** Radiology, Clinica Universidad de Navarra, Clinica Universidad de Navarra - Pamplona/ES
Conclusion

In conclusion, the addition of a second diagnostic technique (DBT and/or US) significantly increased the sensitivity and the AUC´s of DM, but decreased the specificity.

Due to the well-known limitations of US, we suggest that in a screening setting the combination DM+DBT offers a high sensitivity with an acceptable specificity.

However, in a clinical setting, where US can be profusely used, the combination DM+US could be a right choice.
References


