Evaluation of incidental lesions detected on breast-MR by means of advanced fusion imaging techniques of real-time MR navigated US.

Poster No.: C-0819
Congress: ECR 2016
Type: Scientific Exhibit
Authors: M. Culiáñez Casas, F. M. Azcón, M. D. García-roa, S. Martínez-Meca, E. Pastor-Pons; Granada/ES
Keywords: Cancer, Diagnostic procedure, Ultrasound, MR, Experimental, Breast
DOI: 10.1594/ecr2016/C-0819

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Aims and objectives

Objectives

Main objective

-Prospective assessment of real-time US co-registered with breast supine contrast-enhanced MRI using a volume navigation technique (RtMR-US), for diagnosis and guided biopsy of incidental breast-MR lesions suspicious of malignancy (ILSM) and not correlated on second-look US.

Secondary objectives

-Improve loco-regional staging of breast cancer.
-Decrease number of MR-guided biopsies.
-Follow-up of non-removed ILSM.
Methods and materials

MATERIAL AND METHODS

1.- Participants

Cases were consecutively selected following our institutional breast cancer management protocol, approved by the multidisciplinary oncology committee on breast cancer. Patients were prospectively recruited among women who presented ILSM on supine contrast-enhanced breast MRI with dedicated coil (CE-MRI) and no correlation on second-look ultrasound.

From May 2011 through September 2015 (54 months) a total of 1470 women underwent CE-MRI. ILSM were revealed in 16% of them, taken as a whole 52 patients with 69 ILSM, representing 3.5% of overall breast-MRI.

Inclusion criteria:

• Patients with ILSM on CE-MRI
• Negative second-look ultrasound for ILSM
• Informed consent agreement.

Definition of ILSM: all BIRADS 4 or 5 lesions and BIRADS 3 lesions when the multidisciplinary breast cancer committee considered biopsy better than follow-up

2.- Breast contrast-enhanced MRI in supine position

Before navigation, CE-MRI was acquired in supine position. Before MRI exam, three soft gel capsules of D-# tocopherol (Vitamin E, 400 UI; Chiesi S.A, Barcelona, Spain) were placed over three lineal skin marks drawn at 3, 9 and 12 o’clock radial to the nipple (Fig. 1). Afterwards MR representation of these capsules was used for MR-US synchronization.

Supine breast MRI was performed using a 1.5T scanner, with upper extremities extended over the head and using a cardiac MRI phased array coil covering both breasts, placing a dedicated mattress in the intermammary line to avoid breast compression.

CE-MRI protocol included a 3D T1 fast spoiled gradient-echo sequence with spectral fat suppression (LAVA) in axial plane (TR/TE= 4,3 / 2,0; flip angle= 12º ; FOW= 38mm; spacing= 0; slice thickness= 1,5 mm; matrix= 350x350; bandwidth= 50,0; acquisition
time= 5`25´´), one pre-contrast and four post-contrast phases (80s between each phase), after automated intravenous contrast administration of gadobutrol (Gadovist 1mmol/ml; Bayer Pharma AG, Berlin, Germany) 0,1ml/kg, 2ml/s, followed by a flush of 20ml of saline solution using an antecubital vein or dorsal metacarpal vein.

3.- RtMR-US: Real-time US co-registered with breast supine contrast-enhanced MRI using a volume navigation technique

Initial breast US using conventional B-mode and posterior RtMR-US were performed with a commercially available US equipment that contains a magnetic tracking system and a special software for real-time volume navigation (LOGIC E9, GE). A conventional 6-15 MHz matrix array linear transducer was used. Before RtMR-US, breast MR images were evaluated on a post-processing console, choosing the arterial vascular phase, which was saved in a universal serial bus (USB) and uploaded in the US equipment as DICOM file.

For RtMR-US exam the volume navigation equipment was assembled. It was composed of: a) two electromagnetic sensors attached to the tip of the 6-15 MHz transducer; b) a portable electromagnetic transmitter that was positioned near the subject under examination. Both parts were connected to a position-sensing unit installed in the US platform that allowed tracking probe position and orientation within the electromagnetic field (Fig. 2).

The patient had to keep the same position she had during the CE-MRI, with upper extremities extended over the head.

First step for navigation was to retrieve from the USB the selected MR images and load them up in the US equipment. Second step was to synchronise volume MR images with real-time US by means of correlation of the following spatial points: the lineal marks on the patient skin with the MR representation of the three soft gel capsules, the nipples and the internal mammary arteries. Once completed, the green square on MR images correlated with the US field of view (Fig. 3). Subsequently RtMR-US was started, with software marking as a GPS the ILSM identified on CE-MRI with the letter T (from target), making easier correlation on US. Color Doppler and elastosonography were also available during navigation exam (Fig. 4 Video 1).

4.- RtMR-US guided biopsy and breast tissue marking

RtMR-US guided biopsy was performed in 45 ILSM using a single use spring-loaded automatic biopsy device with double shoot mechanism (ACECUT, Leleman S.L, Valencia, Spain), 14-gauge x 11mm or 22mm.

After biopsy a titanium tissue marker was placed (Fig. 4).
5.- **Subsequent breast marker control** with craniocaudal and lateral mammographies and non-contrast enhanced MRI in some cases (images acquired on T1W GRE fat-sat).

6.- **Lesions classification**

On account of the histological results lesions were classified as benign or malignant. All lesions that did not any required treatment were considered as benign. Carcinoma in situ and other preinvasive lesions were classified as malignant.

7.- **Lesions follow-up**

Follow-up was performed for a period between 3-51 months (average of 25,7 months). Mammography and ultrasound were the elective techniques, leaving MR for some selected cases.

8.- **Data analysis**

- Descriptive evaluation of lesions regarding to their location, shape on US and MRI (nodules in both techniques, enhancement areas on MRI and distortion areas on US), size and BIRADS staging.
- For quantitative data were calculated dispersion and central tendency measures (mean, standard deviation, median, interquartile range, minimum and maximum values); for qualitative data, absolute and relative frequency was estimated.
- Association between quantitative data was evaluated using the \( \chi^2 \) test or Fisher’s exact test. The concordance between different imaging techniques was evaluated using \( \kappa \) index. Sensitivity, specificity, positive predictive value and negative predictive value were also calculated.
- Statistical significance was defined as \( p < 0.05 \). Statistical analysis was performed using IBM SPSS statistics 19.0.
Fig. 1: Fig.1 Preparation of the patient before supine breast MRI. Vitamin E soft gel capsules (white arrows) used for US-MRI co-registration placed over lineal skin marks (black arrow) on the patient’s right breast.

© Virgen de las Nieves - Granada/ES

Fig. 2: Fig. 2 US and RtMR-US system. a Electromagnetic sensors on the tip of the probe (white arrows). b Electromagnetic transmitter (black arrow). c Connection unit between electromagnetic transmitter, sensors and the navigation system.
Fig. 3: Images fusion and synchronization testing. The US equipment screen splits into two images, the one in the right real-time US (A), the one in the left MRI (B). Note the green square on image B that matches the US field of view on image A. In this case the subclavian artery and vein were used to test synchronization.

Fig. 4: Video 1. The green mark "T+" (from target), used to point on MRI the ILSM, is also depicted on US images for an accurate correlation. As we move the transducer...
away or closer to the ILSM, the "+" sign is replaced from the "T" mark for a green square that get bigger or smaller depending on our distance to the lesion. Breast elastography is also available. During guided biopsy the "T+" size is modified due to compresion, which do not disturb the procedure. Finally a titanium breast tissue marker is placed.

© Virgen de las Nieves - Granada/ES
Results

1.- Findings on CE-MRI

A total of 69 ILSM were detected among the 52 patients recruited for the study. Clinicopathologic information of patients as well as ILSM features on MRI are summarized in table I.

Correlation between BIRADS categorization on MRI and histological results is depicted in table II. Histological results from biopsy or surgery were available for 57 of the 69 ILSM (47 biopsies and 10 surgical resections). CE-MRI accuracy results for BI-RADS categorization of ILSM attending to their likelihood of malignancy were S 100%, E 46.2%, VPP 68.9%, VPN 100%. Detection rate was 75.4%. Agreement between both techniques was moderated, $k = 0.482$ (95% CI [0.281-0.684]; $p$ # 0.001).

2.- Findings on RtMR-US

A total of 56 ILSM were demonstrated on RtMR-US. Figure 5 shows the study flowchart including patients recruited and ILSM distribution according to BIRADS categorization and their histological results or follow-up outcome.

13 ILSM were not detect on RtMR-US (false negatives), 8 benign lesions and 5 malignant lesions.

Conventional ultrasound sensibility for detection of incidental lesions was 82.2% (319/388) while the added value of RtMR-US increased this number to 96.6 % (375/388). Agreement between both techniques was low, $k = 0.276$ (95% CI [0.155-0.397]; $p$ # 0.001). Figs 6-9 illustrate some cases.

3.- Morphologic features of ILSM on RtMR-US

Among 69 ILSM, 32 (46.4%) were nodules, 23 (33.3%) were correlated with distortion areas and 14 (20.3%) were not detectable. Comparison between MR and US morphologic features demonstrated better agreement regarding to nodules (57.5%) than enhancing or distortion areas (41.4%). However these differences were not statistically significant ($\chi^2$ test, $p=0.09$), as well as agreement, $k = 0.243$ (95% CI [-0.157-0.070]; $p=0.07$). Nine enhancing areas (31%) depicted on CE-MRI were correlated with nodules on RtMRI-US (Fig. 8 y 10).
4.- Histological results after core-needle RtMR-US guided biopsy

A total of 47 ILSM were sampled, results are summarized in table III. Correlation between BIRADS categorization of ILSM biopsied using RtMRI-US and histologic results. Sensibility 90.9%, specificity 68%, PPV 71.4%, NPV 89.5%. k= 0.580 (95% CI [0.356-0.803]) (p<0.001). Diagnostic accuracy: 78.72%.

RtMR-US sensitivity for diagnosis of benign and malignant lesions was 81,2% and 74,4% respectively. For a positive result on RtMR-US the likelihood of malignancy is 48,2% (positive predictive value), whereas a negative result on his technique is correlated with benignity in 61,5% of cases (negative predictive value). RtMR-US allow accurate categorization of ILSM as malignant (p<0.002), (table IV).

RtMR-US contribution to breast cancer staging is summarized on Fig.11:

• 4 patients with occult breast carcinoma.
• 7 multicentric breast carcinomas.
• 3 multifocal breast carcinoma.
• 1 multifocal and bilateral breast carcinoma.
• 5 bilateral breast carcinoma.
• 2 recurrences of breast carcinoma.

In conclusion, 22 patients (42,3%) had their staging and therapeutic approach changed due to the results above describe. As for the other 30 patients remaining (57,7%), the result was benign.

5.- Non-detected ILSM on RtMR-US

Among all ILSM detected on CE-MRI, 13 (18,8%) were not identified on RtMR-US. Regarding to their BIRADS categorization:

• 7 ILSM BIRADS-3: all benign. In 2 cases MR-guided biopsy was performed, revealing a focal adenosis and a fibroadenoma respectively. As for the other 5, their follow-up (average time 22,8 months, range 5-42 months) has shown no change.
• 6 ILSM BIRADS 4-5: Two of them were sampled by MR-guided biopsy (1 benign and 1 malignant) and 4 were surgically removed, all malignant.

In summary, 4 ILSM (3 patients, one of the with two lesions) sample by MRI guided system (5.8%), revealing 1 invasive ductal carcinoma and 3 benign lesions. 4 ILSM surgically removed during mastectomy or tumorectomy in the frame of already known multicentric or multifocal carcinomas.
4.- Benign ILSM on RtMR-US follow-up

Among 69 ILSM, 37 (54%) were considered benign after RtMR-US. 28 of them had histological confirmation, leaving during the tissue sampling procedure a titanium marker for follow-up (average time 28.6 months, range 5-51 months), none of these 28 changed. The other 9 lesions were reconsidered as benign given their morphologic features on RtMR-US, with no biopsy, and undergone for follow-up (average time 17.5 months, range 3-42 months).

There were 2 false negatives on RtMR-US, that represent 5.4% of overall lesions considered benign (37):

- 1 ILSM BIRADS-3 whose biopsy revealed an invasive ductal carcinoma, confirmed as a multifocal carcinoma after tumorectomy (Fig. 12).
- 1 ILSM BIRADS 4-5 whose histological result after RtMR-US guided biopsy was reported as fibrosis. Mastectomy was performed in the context of a multicentric invasive ductal carcinoma revealing its correlation with another area of malignancy.

Fig. 13 depicts one case with bilateral progression after neoadjuvant chemotherapy, while an ILSM initially categorized as BIRADS 4-5 and afterwards histologically reported as adenosis showed no change during the same period.

5.- RtMR-US limitations

- The technique requires a learning curve for optimal results, but otherwise it is easy and consistent.
- Synchronization is more complicated in cases with high volume breast, especially regarding to lower-outer quadrants, more susceptible to changes in the position.
- If the patient or the magnetic field move during the procedure, synchronization between both techniques is lost and must be restarted.
- Interventional procedures guidance (as guided biopsy or tissue marker placement) may need changes in patient position to avoid complications. In such circumstances they could be performed without synchronization once the lesion has been identified (Fig. 14). Over time this limitations are expected to be overtaken by development of new tracker systems already available for US navigation with CT images.
<table>
<thead>
<tr>
<th>Clinicopathologic information of patients</th>
<th>N = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, range)</td>
<td>53 (34-80)</td>
</tr>
<tr>
<td>Indications for prone CE-MRI</td>
<td></td>
</tr>
<tr>
<td>- BC* staging</td>
<td>41 (79%)</td>
</tr>
<tr>
<td>- BC follow-up and high risk patients</td>
<td>7 (13,5%)</td>
</tr>
<tr>
<td>- Unknown primary BC</td>
<td>4 (7,5%)</td>
</tr>
<tr>
<td>Breast size</td>
<td></td>
</tr>
<tr>
<td>- Normotrophic</td>
<td>36 (70%)</td>
</tr>
<tr>
<td>- Hypertrophic</td>
<td>9 (17,3%)</td>
</tr>
<tr>
<td>- Hypoplastic</td>
<td>7 (12,7%)</td>
</tr>
<tr>
<td>ILSM location</td>
<td></td>
</tr>
<tr>
<td>- Right breast</td>
<td>23 (44,3%)</td>
</tr>
<tr>
<td>- Left breast</td>
<td>14 (26,9%)</td>
</tr>
<tr>
<td>- Multicentric</td>
<td>6 (11,5%)</td>
</tr>
<tr>
<td>- Bilateral</td>
<td>4 (7,7%)</td>
</tr>
<tr>
<td>- Bilateral + Multicentric</td>
<td>3 (5,8%)</td>
</tr>
<tr>
<td>- Multifocal</td>
<td>2 (3,8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesions on CE-MRI</th>
<th>N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures (mm): mean, median, range</td>
<td>12, 9, 4-58</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
</tr>
<tr>
<td>- Nodule</td>
<td>40 (58%)</td>
</tr>
<tr>
<td>- Enhancing area</td>
<td>29 (42%)</td>
</tr>
<tr>
<td>BIRADS</td>
<td></td>
</tr>
<tr>
<td>- 3</td>
<td>19 (27,5%)</td>
</tr>
<tr>
<td>- 4 &amp; 5</td>
<td>50 (72,5%)</td>
</tr>
</tbody>
</table>

**Table 1**: Table I. Clinicopathologic information of patients and characteristics of lesions on CE-MRI. *BC: breast cancer.*

© Virgen de las Nieves - Granada/ES
Table 2: Table II. Correlation between BI-RADS categorization of ILSM detected on CE-MRI and histological results as benign or malignant lesions. CE-MRI accuracy for BI-RADS categorization of ILSM attending to their likelihood of malignancy: S 100%, E 46.2%, VPP 68.9%, VPN 100%. Detection rate was 75.4%. Agreement between both techniques was moderated, # = 0.482 (95% CI, 0.281-0.684; p # 0.001).

© Virgen de las Nieves - Granada/ES

Fig. 5: Fig 5. Study flowchart. RtMR-US results.

© Virgen de las Nieves - Granada/ES
**Fig. 6:** 67-year-old woman presenting primary invasive ductal carcinoma in the lower-inner quadrant of the right breast and a 3mm ILSM in the upper-inner quadrant of the same breast. Note correlation between RtMR-US and prone breast CE-MRI.

© Virgen de las Nieves - Granada/ES
Fig. 7: Fig 7. A. RtMR-US tracking system working as GPS. Once the ILSM is marker on the MRI as target (green "T"), the 2.5mm lesion is correlated on US (arrow). Variation in depth is explained due to tissue compression. B. US elastography depicts the entire nodule shaded blue, consistent with stiffness. C. RtMR-US guided biopsy. After histological analysis the nodule was reported as in-situ lobulillar carcinoma and the patient had a double tumorectomy guided by two breast anchors.

© Virgen de las Nieves - Granada/ES
Fig. 8: Fig. 8. 46-year-old patient, with a primary lesion diagnosed as invasive ductal carcinoma (*), presented 2 incidental lesions in the same breast: one benign nodule in the upper-inner quadrant (blue arrow) and one ILSM in the lower-inner quadrant (red arrow). Correlation between RtMR-US and prone MRI revealed that the ILSM is observed as an enhancing area on MRI and with a pseudonodular shape on US. Final histological result was consistent with invasive ductal carcinoma, thereby the patient required mastectomy due to multicentric carcinoma.

© Virgen de las Nieves - Granada/ES
**Fig. 9**: Fig 9. 70-year-old woman with metastatic axillary lymph node and initially undetected breast carcinoma on mammography and ultrasound. An ILSM was revealed at prone CE-MRI but not detected on second-look US. (A) By means of RtMRI-US, the 5mm nodule on CE-MRI (arrow head) was correlated on US (white arrow), presenting same location and shape. The white box depicted on MR images represents the ultrasound field of view. (B) RtMRI-US guided biopsy of the nodule. Final diagnosis: invasive lobulillar carcinoma.

© Virgen de las Nieves - Granada/ES
Fig. 10: Fig 10. Morphologic features on CE-MRI and US

© Virgen de las Nieves - Granada/ES

<table>
<thead>
<tr>
<th>Correlation between BIRADS categorization of ILSM biopsied using RtMRI-US and histologic results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIRADS 4-5</td>
</tr>
<tr>
<td>Malignant lesions</td>
</tr>
<tr>
<td>- Invasive ductal carcinoma</td>
</tr>
<tr>
<td>- Invasive lobulillar carcinoma</td>
</tr>
<tr>
<td>Benign lesions</td>
</tr>
<tr>
<td>- Fibrocystic disease</td>
</tr>
<tr>
<td>- Fibroadenoma</td>
</tr>
<tr>
<td>- Intramammary lymph node</td>
</tr>
<tr>
<td>- Fibrosis</td>
</tr>
<tr>
<td>- Haemorragic cyst</td>
</tr>
<tr>
<td>- Non-atypical intraductal hyperplasia</td>
</tr>
<tr>
<td>- Foreign body granuloma</td>
</tr>
<tr>
<td>N</td>
</tr>
</tbody>
</table>

Table 3: Table III. Correlation between BIRADS categorization of ILSM biopsied using RtMRI-US and histologic results. Sensibility 90.9%, specificity 68%, PPV 71.4%, NPV 89.5%. Kappa index: 0.580, IC95% [0.356-0.803] (p<0.001). Diagnostic accuracy: 78.72%

© Virgen de las Nieves - Granada/ES
Table 4: Table IV. Correlation between ILSM identified on RtMRI-US and their histological results as benign or malignant. Detection rate 81,2% (56/69). S 84,4%; E 21,6%; PPV 48,2%; NPV 61,5%.

© Virgen de las Nieves - Granada/ES

Contribution of RMRt-US

Fig. 11: Fig 11. RtMR-US contribution for breast cancer staging. In 22 patients (42,3%) there was a change in the cancer stage and therapeutic approach. The other 33 patients (57,7%) had benign lesions.

© Virgen de las Nieves - Granada/ES
**Fig. 12:** Fig. 12. RtMR-US false negative. During breast cancer staging was noted an ILSM categorized as BIRAD-3 on RtMR-US, whose histological analysis revealed a invasive ductal carcinoma (white arrow).

© Virgen de las Nieves - Granada/ES

**Fig. 13:** Fig. 13. A. RtMR-US performed for breast cancer staging shows an ILSM (pink arrows), subsequently biopsied and reported as adenosis. B: Bilateral progression after neoadjuvant chemotharapy with no change of the ILSM (pink arrow).

© Virgen de las Nieves - Granada/ES
Fig. 14: Fig 14. RtMR-US guided biopsy and marker placement. Changes in patient position lead to loss of synchronization.

© Virgen de las Nieves - Granada/ES
Conclusion

CONCLUSION

- RtMR-US increases ultrasound detection of ILSM, presenting high sensibility and negative predictive value for a technique whose aim is to reevaluate lesions otherwise not recognizable.
- RtMR-US improves loco-regional breast cancer staging and allows detection of occult carcinomas.
- RtMR-US enable guided biopsy of ILSM, reducing number of MR-guided biopsy, saving costs and
- ILSM categorized as BIRADS-3 and not identified on second-look ultrasound are probably benign.
- Some enhancing areas on MRI correlate with nodules on US.
- During this work the absence of recurrences through non-treated ILSM follow-up allowed us to establish RtMR-US capabilities.
References


