# The influence of preoperative MRI in early breast cancer: gold standard



Ann Ital Chir, 2020 91, 2 144-153 pii: S0003469X19031178 free reading: www.annitalchir.com

Daniela Messineo\*, Luciano Izzo\*\*, Massimo Codacci Pisanelli\*\*, Francesco Razionale\*\*, Sara Izzo\*\*\*, Paolo Izzo\*\*

\*Department of Radiological Sciences, Oncology and Pathology, "La Sapienza" University of Rome, Italy \*\*Department of General Surgery "Pietro Valdoni", "La Sapienza" University of Rome, Italy \*\*\*Multidisciplinary Department of Medical-Surgery and Dental Specialities Plastic Surgery Units, University "Luigi Vanvitelli", Naples, Italy

## The influence of preoperative MRI in early breast cancer: gold standard

BACKGROUND: Aim of this study was to evaluate the impact of presurgical breast MRI on the surgical management of selected patients with early-stage breast cancer, who were candidates for BCT. MATERIALS AND METHODS: The trial was built up according to the major European Breast Society. In additional foci

MATERIALS AND METHODS: The trial was built up according to the major European Breast Society. In additional foci classified as BI-RADS 3-4 (4a, 4b, and 4c), a targeted second-look US study was performed.

RESULTS: A total of 123 patients underwent presurgical breast MRI. Therapeutic strategy established based on MRI was appropriate in 83.8% of cases. Analysis carried out on the subgroup of patients with dense breast showed that additional foci were found in 41.9% and a greater local extension of the index lesion in 6.4%.

CONCLUSION: The results obtained in the subgroup of patients with high breast density suggest the importance of a sensitive tool such as MRI in the local staging of breast cancer before treatment planning.

KEY WORDS: Breast cancer, BI-RADS, Histological diagnosis, Mammography MRI

#### Introduction

Breast-conserving treatment (BCT), including wider local excision or quadrantectomy plus radiotherapy, is generally accepted as a preferable alternative to mastectomy for tumors up to 3 cm in diameter since there is no significant difference between mastectomy and BCT in terms of mortality rate  $^{27}$ .

Surgical treatment within the framework of BCT has always aimed at complete excision of the tumor tissue and at obtaining clear margins. In order to obtain the best results in BCT and to reduce the risk of recurrence, the accurate local staging of breast cancer is essential (extent of index lesion, multifocality, multicentricity, contralateral cancer) <sup>44,57</sup>. Various studies have demon-

Pervenuto in Redazione: Luglio 2019. Accettato per la pubblicazioe Settembre 2019

Correspondence to: Luciano Izzo, Dipartimento di Chirurgia "P. Valdoni", Università degli Studi di Roma "La Sapienza," Via G. Tomasi di Lampedusa 9, 00144 Rome, Italy (e-mail: luciano.izzo@uniroma1.it)

strated that breast Magnetic Resonance Imaging (MRI) has a higher sensitivity in local staging than conventional imaging, such as X-ray mammography (X-RM) and breast ultrasound (US) <sup>18,21,55</sup>, particularly in conditions where the sensitivity of these techniques is reduced, e.g. in women with elevated mammographic density. In these patients, US examination can reduce the number of 16,36 false negatives produced by mammography However, a significant number of multifocal and multicentric breast carcinomas are still missed at routine diagnostic imaging <sup>17</sup>. Mammographic density has consistently been one of the strongest risk factors for breast cancer, with risk estimates that are three- to five-fold greater for women with high breast density 40,64. According to international oncology guidelines <sup>50</sup> MRI as a staging procedure in women with breast cancer is optional, but according to European Breast Cancer Council (EBC council) and European Society of Breast Cancer Specialists (EUSOMA), and EUROPA DON-NA: The European Breast Cancer Coalition 14,50,60 breast MRI staging before treatment planning presents potential advantages and is indicated in the following cases:

(1) patients newly diagnosed with invasive lobular cancer; (2) patients at a high risk for breast cancer; (3) patients under 60 years of age with discrepancy in size >10 mm between X-ray mammography and US with expected impact on treatment decision; (4) patients eligible for partial breast irradiation (PBI) on the basis of clinical breast examination (CBE) and conventional imaging.

EUSOMA furthermore recommends preoperative MRI as a scientific research issue in:

(1) patients with dense breasts: 1a) dense breast in young women (<40 years of age); 1b) dense breast associated with intermediate lifetime risk (15–20%) for other factors, (2) patients with unilateral unifocal pure ductal carcinoma in situ (DCIS) at conventional imaging (to exclude synchronous ipsilateral or contralateral invasive cancers).

The BI-RADS 3 (2013) defines the lesion benign probably and recommended a short-term imaging follow-up of 6 months for two years. If a BI-RADS 3 lesion shows any change during follow up, it will change into a BI-RADS 4 or 5 and biopsy had to be performed.

In the BIRADS 4, the findings became suspicious and the abnormality needs a biopsy. So according to with the BIRADS 4a is mild suspect, BIRADS 4b is moderate suspect, and BIRADS 4c is severe suspect with high suspicion for malignancy statistically the risk is between > 50% to < 95% likelihood of malignancy  $^{14,66}$ .

Aim of this study was to evaluate the impact of presurgical breast MRI in the operative management of selected patients with unilateral unifocal early breast cancer, candidates for BCT. Subsequently, this impact was evaluated in subgroups of patients with high mammographic density.

# Materials and Methods

Ethical approval for this single-center, observational study was granted by the Medical Research Ethics Committee of our institution, and written informed consent was obtained from all patients.

The sample was built up from January 2016 to November 2018 at the Department of Radiological Sciences, Oncology, and Pathology, "Sapienza" University of Rome among women with unilateral unifocal early breast cancer. The diagnosis was based on clinical examination, X-RM, and the US and in some cases also on needle biopsy; all patients were candidates for BCT. The initial palpable lesion and/or suspicious mammographic or US findings are in the following analysis called the "index lesion".

In all cases, conventional XRM was performed using digital image formation and computed radiography.

At least two views per breast were obtained. In addition to this, further views or spot magnification were performed at the discretion of the interpreting radiologist. The US and Doppler US studies were performed by the same radiologist according to previously reported standards <sup>54</sup>.

Mammograms and US were interpreted in accordance with the guidelines of the American College of Radiology (ACR) Breast Imaging Reporting and Data system (BI-RADS<sup>®</sup>) <sup>14</sup> by a radiologist with 20 years of experience in the field of breast imaging, blinded to the clinical data. Based on the BI-RADS lexicon, patients were then assigned to one of the four categories of breast parenchymal density distribution <sup>15</sup>: type 1, the breast is almost entirely fat (glandular parenchyma <25% of the total area of both breasts); type 2, scattered fibroglandular densities (25%-50%); type 3, heterogeneously dense breast tissue (51%-75%); type 4 extremely dense (> 75% glandular). It is a well-known fact that sensitivity of mammography is reduced in type 3 and 4 (50.5%) and the patients participating in our study were therefore divided into two groups: dense breast (DB) which included BI-RADS type 3 and 4 and no dense breast (NDB) which included BI-RADS type 1 and 2.

Before MRI, US-guided a needle biopsy of the index lesion was in some cases performed by an expert to clarify diagnostic doubt.

After recruitment, the women were interviewed by a physician to collect information including: age at diagnosis of breast cancer, family history of breast cancer (positive: at least two first-degree relatives age  $\leq 50$ ), positive for BRCA1/2 gene mutations (subjects with positive test for one full-term pregnancy), lactation for at least 3 months (yes/no).

Patient deleterious mutation in breast cancer susceptibility genes BRCA1, BRCA2), age at menarche, menopausal status (absence of menstrual cycles for at least 12 months), parity (nulliparous or with at least population was selected according to the following inclusion criteria:

-mammography: elevated mammographic density (BI-RADS 3 or 4), suspicious microcalcifications (pleomorphic or heterogenous calcifications (granular) or fine linear, fine linear branching (casting) calcifications);

- discordant mammographic and US outcome in the identification of the index lesion and/or its dimensions (significant if >10 mm)

- histology of the index lesion (histological diagnosis of invasive lobular carcinoma, ILC);

– hereditary factors (positive for BRCA1/2 gene mutations, with at least two first-degree relatives age  $\leq 50$  years with a clinical history positive for breast carcinoma);

- characteristics of the lesion and treatment plan: the study includes only women with unilateral unifocal lesions smaller than 3 cm in diameter for whom the interdisciplinary medical team had indicated wider local excision based on conventional imaging findings.

Patients were excluded if they presented with contraindications to MRI (pace-maker, ferromagnetic clips, claustrophobia, gadolinium allergy, acoustic hearing implants and intraocular lens implants incompatible with the 1.5T magnetic field) if they were eligible for PBI on the basis of CBE and conventional imaging and/or eligible for radiotherapy or neoadjuvant chemotherapy. Patients who were eligible for this study underwent MRI maximum of 30 days from diagnosis of unifocal breast cancer.

In premenopausal women, presurgical breast MRI was performed on day 6-13 of the menstrual cycle, including those who were receiving oral contraception <sup>57</sup>. Patients receiving hormone replacement therapy underwent MRI minimum of 4 weeks after discontinuation of treatment <sup>51</sup>.

The examination was carried out using a 1.5 T magnet (Avanto, Siemens Medical Solutions, Germany) equipped with a bilateral multichannel dedicated coil with an integrated compression mechanism. The patient was positioned face down on the moveable examination table, the breasts were placed inside the dedicated coil in order to avoid an incorrect position which might have prevented the study of the entire mammary gland. The built-in compression mechanism guaranteed the stability of the breasts in the coil to minimize any motion artifacts.

Morphological study was performed using T2-weighted short tau inversion recovery (STIR) unenhanced axialplane sequences, whereas dynamic study was carried out in six consecutive T1-weighted FLASH 3D DYNAMIC (FL 3D DYN) sequences in the axial plane after intravenous injection of paramagnetic contrast medium followed by a T1-weighted Fat Saturation (FS) sequence in the coronal plane.

T1-weighted sequences presented the following characteristics: Repetition Time (TR) = 4.23 msec; Echo Time (TE) = 1.24 msec; flip angle =  $10^{\circ}$ ; matrix =  $3.84 \times 3.84$ ; pixels =  $1 \times 1 \times 1$ ; Field of View (FoV) =  $380 \times 380$ ; slice thickness = 1mm; interslice gap = 0.2 mm.

T2-weighted sequences presented the following characteristics: TR = 5280 msec; TE = 51 msec; flip angle =  $160^{\circ}$ ; matrix = 384 x 384; pixels = 0.9 x 0.9 x 4; FoV = 340 x 340; slice thickness = 4mm; interslice gap = 0.8 mm.

Contrast medium was Gadoterate Meglumine (Dotarem<sup>®</sup>, Guerbet, S.p.A.) administered in a concentration of 0.1 mmol/kg; it was injected through a 20 G intravenous cannula at the rate of 2 ml/sec using an automatic injector and followed by infusion of 20 ml saline solution at the same speed.

Image post-processing included temporal subtraction (contrast-enhanced minus unenhanced image) for dynamic studies without fat saturation and maximal intensity projection (MIP). Dynamic analysis with the generation of percent enhancement versus time curves was performed through the positioning of regions of interest (ROI) for all identified enhancing lesions with a diameter  $\geq$  5 mm and mass-like morphology according to the MRI BI-RADS classification <sup>13</sup>.

Analysis of the obtained MRI results took the following into account:

1) Shape (round, oval, lobular, irregular), margin (circumscribed, microlobulated, obscured, indistinct, spiculated) and the characteristics of the baseline signal in T1- and T2-weighted sequences of the main index lesion and possible additional foci (iso-hypo-hyperintense compared to the glandular parenchyma).

2) Kinetics of enhancement assessed by the intensity/time curve.

3) Local extension. Criteria applied to establish the local extent of disease were a) size of the index lesion defined as the largest diameter of the lesion; b) infiltration of the skin; c) infiltration of the pectoralis major muscle; d) infiltration of the nipple. With regard to size, a difference of >10 mm between the size measured at conventional imaging techniques and the size measured at MRI was considered significant  $^{29,30}$ .

4) Presence of additional foci were considered only if >5 mm. Multifocality was diagnosed in the presence of multiple foci of malignancy in the same breast quadrant. Multicentricity was diagnosed when two or more foci of disease occupied more than one quadrant. Bilaterality was diagnosed if neoplastic lesions were found in both breasts (bilateral synchronous breast cancer) <sup>13,24</sup>. All lesions were classified in one of the six BI-RADS categories according to their probability of being malignant <sup>13</sup>.

Targeted second-look ÚS was performed to identify MRI findings classified as BI-RADS 3-4, and US-guided needle-biopsy procedure was performed on additional foci confirmed at second-look US. In cases where additional foci were classified as BI-RADS 5 and/or the index, lesion was larger than established by conventional imaging techniques, no further diagnostic investigation was performed.

The multidisciplinary team consisting of a radiologist, a pathologist, a surgeon/gynecologist, and an oncologist reviewed all cases establishing a therapeutic strategy in view of the evidence provided by MRI. Total treatment delay due to preoperative MRI and possible workup did not exceed one month.

Histological examination of the surgical specimen and particularly the analysis of tumor infiltration of the resection margins was the standard for determining the appropriateness of therapy. The surgical procedure was considered appropriate in the presence of disease-free resection margins.

# Results

The sample was selected from 374 patients with clinical, mammographic, US and in some cases the histological diagnosis of unilateral unifocal breast cancer; all were candidates for conservative surgery (wider local excision or quadrantectomy).

A total of 206 patients with unifocal breast cancer < 3 cm in diameter for whom the multidisciplinary team had planned wider local excision based on conventional imaging findings were selected; of these patients, 123 were found eligible for this study and underwent presurgical breast MRI. The main characteristics of the eligible patients are presented in Table I.

Variables			Sample (N= 123)
Age at cancer diagnosis (years; mean)			50.2 ± 10.4
Menopausal status (%):	menopause		55.2%
-	No menopause		44.8%
Parity (%):	Nulliparity		43.9%
-	At least one full-term pregnancy		56.1%
Age at menarche (years, mean)	13.6 ± 3.8		
Lactation for at least 3 months (yes	, %)		42.2%
Mammographic breast density (%)			
BI-RADS 1-2 (non dense breast)			49.5%
BI-RADS 3-4 a, b, and c (dense breast)			50.5%
	BI-RADS 3		2.4%
	BI-RADS 4a		8.3%
	BI-RADS 4b		9.3%
	BI-RADS 4c		30.5%
Suspicious microcalcifications	15.4%		
Discordance (>10 mm) between			
mammographic and US detection			
of the main index lesion and/or its dimensions (%)			13%
Positive for BRCA1/2 (%)			2.4%
First-degree family history of breast carcinoma* (%)			22.7 %
ILC**			4%

TABLE I - Main characteristics of the enrolled patients and indications for breast MRI.

\*At least 2 first-degree relatives diagnosed with breast carcinoma at age 50. \*\* Assessed by needle biopsy of the index lesion before MRI.

All MRI examinations were performed according to EUSOMA guidelines and were considered technically adequate and of good diagnostic quality.

Regarding MRI-guided local staging, there was concordance with the results obtained by conventional imaging techniques in 52%, whereas MRI provided a better local staging in 48%:

- in 6.4% MRI showed the greater local extent of the index lesion (in 0.8% for infiltration of the nipple, in 1.6% for infiltration of the skin, in 1.6% for infiltration of the pectoralis major muscle and in 2.4% because the lesion was >10 mm larger than measured at conventional imaging);

- in 41.6% MRI detected further post-contrast enhancements of > 5 mm in diameter (multifocal carcinoma in 21.9%, multicentric carcinoma in 16.5% and bilateral carcinoma in 3.2 %).

In 10.7%, morphology and dynamics of the additional foci were highly suggestive of malignancy (BI-RADS 5), whereas the remaining 30.9% were classified as BI-RADS 3-4 and underwent second-look US. In 9.7% second-look US was negative, whereas the additional lesions detected by MRI were confirmed in 21.2% cases, and US-guided needle biopsy was therefore performed. Histological examination was positive for carcinoma in 17.1% and for typical ductal hyperplasia in 4.1% cases. Overall, 13.8% of additional foci were not confirmed by second look and needle biopsy.

Re-evaluation of each case by the multidisciplinary team led to confirmation of therapeutic strategy in 65.8% (9.7% as additional lesions were not confirmed after targeted second-look US; 4.1% as US-guided needle biopsy of additional focal lesions was negative (typical ductal hyperplasia); 52% as MRI confirmed local staging established by conventional imaging techniques).

Histological examination of the surgical specimen showed that resection margins were free of disease in 54.5% thus confirming that therapeutic strategy was appropriate; in 11.3% resection margins showed neoplastic infiltration and repeat surgery was required.

More extensive surgery was performed in 34.2% including 6.4% due to the greater local extent of the unifocal lesion and 27.8% due to the presence of additional foci, classified as BI-RADS 5 in 10.7% or confirmed by needle biopsy in 17.1%.

Planned therapeutic strategy was substituted with quadrantectomy plus radiation therapy in 20.3% due to greater local extent of the index lesion (6.4%) or multifocality (13.9%) (Fig. 1), with unilateral mastectomy in 10.7% due to multicentricity (Fig. 2) and with bilateral mastectomy in 3.2% due to bilaterality.

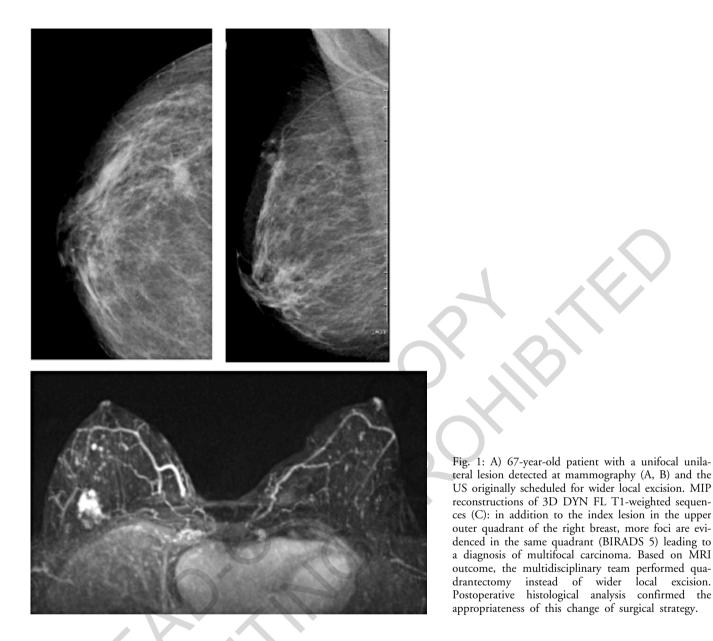
The modified therapeutic strategy was assessed by histological examination of the surgical specimens showing appropriateness in 29.3%:

- 13.1% conversion from wider local excision to mastectomy (mono-bilateral) due to true positive findings;

- 16.2% conversion from wider local excision to quadrantectomy due to true positive findings.

Histological examination did not confirm MRI finding of higher local staging in 4.9%:

- 0.9% conversion from wider local excision to mastectomy (mono-bilateral) due to false positive findings;



- 4% conversion from wider local excision to quadrantectomy due to false positive findings.

In total, presurgical breast MRI led to correct treatment in 83.8%, to overtreatment in 4.9% and undertreatment in 11.3%.

In the subgroup of patients with dense breasts (50.5% of the sample) detection of additional foci in 41.9% and greater local extent of the index lesion in 6.4% led to overstaged local disease in 48.3%. Additional foci were classified as BI-RADS 5 in 8%, confirmed by second-look US and needle biopsy in 25.9% whereas the remaining 8% were not confirmed at second-look US.

More extensive surgery was performed in 40.3%, appropriateness of modified surgical approach was 35.5% leading to overtreatment in 4.8% (Fig. 2).

### Discussion and Conclusions

Surgical planning is commonly based on clinical examination and conventional breast imaging techniques, such as mammography and US, although the impact of breast MRI on the presurgical staging of patients with primary breast cancer is evolving <sup>4,27,34,35,37,48</sup>].

The value of breast MRI is based on the capability of this modality to depict: (a) multicentric and multifocal disease <sup>4,5,23,51,53]</sup>, (b) an invasive component in ductal carcinoma in situ lesions <sup>26</sup>, (c) the tumor in a three-dimensional way <sup>26,53</sup>, and (d) cancer in dense breast tissue <sup>4,5,28,31</sup>. Thus, MRI has facilitated improved local staging (extent of index lesion, multifocality, multicentricity, contralateral cancer) <sup>13,18,19,33,49,50]</sup> and safer breast-conserving surgery in patients with breast lesions, the-

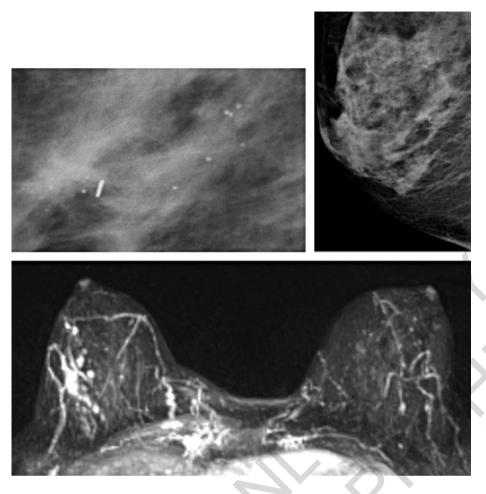


Fig. 2: A) 54-year-old patient with high mammographic density (BI-RADS 3) and suspicious microcalcifications detected at mammography (A, B) in the lower inner quadrant of the right breast. MIP reconstructions of 3D DYN FL T1-weighted sequences (C): in addition to the main lesion located in the lower inner quadrant of the right breast, more foci are evidenced in the same quadrant (BI-RADS 4) involving also the upper outer quadrant. Diagnosis: multicentric carcinoma confirmed by second look and needle biopsy. The patient underwent a unilateral mastectomy. Postoperative histological analysis confirmed the appropriateness of this modified therapeutic strategy.

reby reducing the risk of local recurrence <sup>20,25</sup>. Furthermore, contrary to initial assumptions, MRI has also proved to be able to detect invasive lobular carcinoma (ILC) and ductal carcinoma in situ (DCIS) as well as the extensive intraductal component (EIC) that can appear as "no mass like" enhancement <sup>22,26,38,41</sup>. MRI also allowed the identification of the involved locoregional lymph nodes <sup>20</sup>.

Numerous studies have been performed to assess the diagnostic performance of MRI in the evaluation of breast lesions <sup>6,9</sup>. Sensitivity and specificity varied widely among the included studies: sensitivity ranged from 0.63 to 1.00, and specificity ranged from 0.21 to 1.00. At a sensitivity of 0.95, the corresponding specificity was 0.67 <sup>45</sup>.

On the other hand, suboptimal specificity of breast MRI often leads to the need for further diagnostic workup (second-look US and US-guided needle biopsy) and changes in therapeutic management have a frequency of about one fifth compared with a well-known lower rate of local recurrence after breast-conserving treatment combined with radiotherapy <sup>18,39</sup>. Furthermore, a more complete local staging of the disease may be associated with a risk of surgical overtreatment. To date, there is no evidence from randomized controlled studies in favor or

against a positive impact of presurgical breast MRI on disease-free or overall survival.

Our results confirm the high sensitivity of MRI in presurgical local staging of breast cancer reported in the literature <sup>63</sup>. In this study, conventional imaging techniques had detected unilateral unifocal early-stage breast carcinoma in all patients, but MRI detected additional foci of ipsilateral disease (multifocal or multicentric) in 38.4%, while contralateral breast lesions were detected in 3.2% with a total value of 41.6%. However, 13.8% of the identified additional foci were not confirmed by second-look US and needle-biopsy but an increased local extension of the index lesion was found in 6.4%.

Surgical management was modified, and more extensive surgery was performed as a result of MRI in 34.2%. This decision proved appropriate in 29.3% with an overtreatment rate of 4.9%. Presurgical breast MRI resulted in confirmation of surgery in 65.8% with an appropriateness rate of 54.5%. Surgical resection margins were positive for malignancy in 11.3% and repeat surgery was therefore required. Overall appropriateness of therapeutic strategy as a result of MRI was 83.8%. Our results confirm the importance of an accurate selection of patients for MRI based on risk factors <sup>50</sup> such as mammographic features, family history of breast cancer and/or histological analysis as indicated in the EUSOMA recommendations <sup>51</sup>. In accordance with these recommendations, patients eligible for PBI based on CBE and conventional imaging were excluded from this study as PBI is not performed in our institution.

The low overtreatment rate due to false positive findings confirms the value of second-look US and needle biopsy of the additional lesions detected by MRI <sup>46</sup>. In our opinion, the combination of patient selection and identification of additional foci using second-look US and needle biopsy is essential for an accurate interdisciplinary assessment and for a correct therapeutic approach, despite the increase in time and costs. However, in the present patient population, the total treatment delay due to preoperative MRI and possible workup did not exceed one month.

In agreement with Sardanelli et al. we suggest that MRI should be performed in patients with dense breasts <sup>50-53</sup>. In the subgroup of patients with dense breast (BI-RADS 3-4) additional foci were detected in 41.9%, and greater local extent of the index lesion in 6.4%. More extensive surgery was performed in 40.3% and conversion of surgical approach was appropriate in 35.5% with an overtreatment rate of 4.8%. Therefore, despite the more frequent detection of additional foci and greater local extension of the index lesion and consequently, more extensive surgery, this subgroup did not show a higher overtreatment rate.

Mammographic density is inversely correlated with mammographic accuracy. Measurement of density conveys information about the difficulty of detecting cancer in a mammogram, and density has therefore been strongly associated with increased breast cancer risk 7,8,58,59, 65. Currently, a widely used density classification scheme is BI-RADS <sup>3</sup>. This qualitative system was not developed to quantify the risk, but to allow an interpreting radiologist to indicate the level of concern that cancer in the breast might be missed on mammography due to masking by dense tissue <sup>2,12,17,43,47,56,58,59,61, 62</sup>. It is wellknown that the sensitivity of mammography is decreased in dense breasts <sup>10,11</sup> and a high BI-RADS score tel-Is a referring physician that other tests less affected by density, such as US <sup>1,16, 36</sup> or MRI might be required. Mammographic density has also consistently been one of the strongest risk factors for breast cancer, and women with dense tissue in 75% or more of the breast have a risk of breast cancer 4 to 6 times as great as the risk among women with little or no dense tissue 18,19, 33.

The main strength of this study was that our center performs more than 150 MRI examinations per year and has extensive experience in conventional breast imaging, i.e. X-RM, breast US, and US-guided needle-biopsy procedures as well as in targeted second-look US to analyze MRI findings missed at conventional imaging prior to MRI. It was furthermore an advantage that histological examination was carried out exclusively by a pathologist specialized in breast diseases.

Technical procedures (MRI protocol and post-processing images) and methodology (MRI was always performed according to the phase of the menstrual cycle and at least 4 weeks after discontinuation of hormone replacement therapy) were performed according to the EUSO-MA recommendations, and a standardized method such as BI-RADS lexicon was employed for the interpretation. Furthermore, changes in therapeutic planning were decided upon by a multidisciplinary team.

Several limitations of this study should be considered. The lack of a control group, the randomization in the selection of patients for presurgical MRI and follow-up makes it impossible to evaluate some parameters, such as the impact of MRI on the risk of repeat surgery and the real benefit of more extensive surgery in case of detection of additional malignant lesions followed by radiotherapy and/or adjuvant systemic chemotherapy or hormone therapy. Mammographic breast density was established by a single radiologist using a qualitative visual system. Patients were classified as "dense breast" based on mammographic density regardless of age and lifetime risk. No statistical analysis was performed to evaluate the association between mammographic density and detection of additional foci and more extensive surgery. The results obtained in the subgroup of patients with dense breasts are therefore merely descriptive.

We did not make a correlation with the subclasses 4 because the studies found did not have a similar sample and therefore were not comparable with the values obtained in the present study.

In conclusion, preoperative MRI remains a hot topic and a complex problem which will probably remain unresolved for several years. We have in our hands a technique which is surely the best option for evaluating ipsilateral disease extent and possible contralateral cancers, but we are not sure that, using this technique, we can provide our patients with a better treatment. We might, in fact, provide a worse treatment, i.e. an avoidable more aggressive treatment.

The present experience confirms the utility of a highly sensitive but non-specific diagnostic tool such as MRI in the presurgical workup of breast lesions. However, in our opinion, an improved advantage/disadvantage relationship includes a careful selection of patients and the US as well as histological confirmation of additional foci detected by MRI.

Changes in therapeutic management resulting from preoperative MRI findings should be decided upon by a multidisciplinary team. Finally, we believe that high breast density should be an indication for MRI as it is a risk factor for breast carcinoma and because it reduces the sensitivity of mammography.

Careful prospective randomized trials are required to determine whether MRI in the preoperative assessment of women with a diagnosis of breast cancer leads to a decrease in tumor recurrence and to determine the costeffectiveness of this approach. MRI restricted to patients with high breast density is appropriate until well-designed randomized controlled trials have established the clinical, psychosocial, and long-term effect of MRI.

#### Riassunto

Questo studio è finalizzato alla valutazione delle conseguenze dell'uso della risonanza magnetica mammaria prechirurgica sulla gestione di pazienti selezionati con carcinoma mammario in fase iniziale, candidati a chirurgia conservativa, ed è stato eseguito secondo i principi della maggiore European Breast Society. In caso di ulteriori focolai classificati come BI-RADS 3-4 (4a, 4b e 4c), è stato condotto un second look mirato con US.

Un totale di 123 pazienti sono stati sottoposti a risonanza magnetica mammaria pre-chirurgica. La strategia terapeutica decisa in base agli esiti della risonanza magnetica è risultata appropriata nell'83,8% dei casi. L'analisi effettuata sul sottogruppo di pazienti con seno denso ha mostrato che nel 41,9% sono stati rilevati ulteriori focolai e una maggiore estensione locale della lesione indice nel 6,4%.

In conclusione i risultati ottenuti nel sottogruppo di pazienti con alta densità mammaria suggeriscono l'importanza di uno strumento sensibile come la risonanza magnetica nella stadiazione locale del carcinoma mammario prima della pianificazione del trattamento.

#### References

1. Miyake T, Kim SJ, Shimoda M, Kagara N, Tanei T, Naoi Y, Shimazu K, Noguchi S: *Diagnostic utility of third-look, contrast-enhanced sonography followed by needle biopsy for mri, but not second-look ultrasonography-detected breast lesions.* Anticancer Res, 2019; 39 (2):915-21; doi:10.21873/anticanres.13194.

2. Akita A, Tanimoto A, Jinno H, Kameyama K, Kuribayashi S: The clinical value of bilateral breast MR imaging: is it worth performing on patients showing suspicious microcalcifications on mammography? Eur Radiol, 2009; 19(9):2089-96. DOI: 10.1007/s00330-009-1396-4.

3. Balleyguier C, Ayadi S, Van Nguyen K, Vanel D, Dromain C, Sigal R: *BIRADS<sup>TM</sup> classification in mammography.* Eur J Radiol, 2007; 61(2):192-94. Epub 2006. DOI: 10.1016/j.ejrad.2006.08.033

4. Bedrosian I, Mick R, Orel SG, Schnall M, Reynolds C, Spitz FR, Callans LS, Buzby GP, Rosato EF, Fraker DL, Czerniecki BJ: *Changes in the surgical management of patients with breast carcino-ma based on preoperative magnetic resonance imaging*. Cancer, 2003, 1;98(3):468-73. DOI: 10.1002/cncr.11490.

5. Berg WA, Gutierrez L, Nessaiver MS, et al.: *Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer.* Radiology, 2004; 233:830-49.

6. Bluemke DA, Gatsonis CA, Chen MH, et al: *Magnetic resonance imaging of the breast prior to biopsy.* JAMA, 2004; 292(22): 2735-742. DOI: 10.1001/jama.292.22.2735.

7. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S, Yaffe MJ: *Mammographic density and the risk and detection of breast cancer.* N Engl J Med, 2007; 356:227-36. DOI: 10.1056/NEJMoa062790.

8. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD: *Mammographic breast density as an intermediate phenotype for breast cancer*. Lancet Oncol., 2005; 6(10):798-808. Breast, 2013; 22(Suppl2):S115-7. doi: 10.1016/j.breast.2013.07.022.

9. Brix G, Henze M, Knopp MV, et al.: Comparison of pharmacokinetic MRI and [18F] fluorodeoxyglucose PET in the diagnosis of breast cancer: Initial experience. Eur Radiol, 2001; 11(10):2058-2070. DOI: 10.1007/s003300100944.

10. Buist DS, Porter PL, Lehman C, Taplin SH, White E: Factors contributing to mammography failure in women aged 40-49 years. J Natl Cancer Inst, 2004; 96:1432-440. DOI: 10.1093/jnci/djh269.

11. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, Geller BM, Abraham LA, Taplin SH, Dignan M, Cutter G, Ballard-Barbash R: *Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography.* Ann Intern Med, 2003; 138:168-75. DOI: 10.7326/0003-4819-138-3-200302040-00008.

12. Ceugnart L, Taieb S, Vennin P, Giard S, Chauvet MP, Chaveron C, Bachelle F, Faivre-Pierret M, Rocourt N, Bercez H, Fauquet I: Role of MRI in the presurgical work-up of breast cancer: Appropriate utilization of MRI as a complement to mammography and ultrasound. J Radiol, 2008; 89(11 Pt 1):1774-779.

13. Derloo E, Deterse JL, Rutgers E et al.: Additional breast lesions in patients eligible for breast-conserving therapy by MRI: Impact on preoperative management and potential benefit of computerized analysis. Eur J Cancer, 2005; 41:1393-1401.

14. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA: ACR BI-RADS<sup>®</sup> Atlas, Breast Imaging Reporting and Data System. Vth edit. Reston: American College of Radiology, 2013.

15. Eberl MM, Fox CH, Edge SB, Carter CA, Mahoney MC: BI-RADS classification for management of abnormal mammograms. J Am Board Fam Med, 2006; 19(2):161-64.

16. Elshof LE, Rutgers EJ, Deurloo EE, Loo CE, Wesseling J, Pengel KE, Gilhuijs KG: *A practical approach to manage additional lesions at preoperative breast MRI in patients eligible for breast-conserving therapy: Results.* Breast Cancer Res Treat, 2010; 124(3):707-15. doi: 10.1007/s10549-010-1064-z. Epub 2010 Jul 22.

17. Enriquez L, Listinsky J: *Role of MRI in breast cancer management*. Cleve Clin J Med, 2009; 76(9):525-32. DOI: 10.3949/ccjm.76a.06043.

18. Fischer U, Baum F, Luftner-Nagel S: *Preoperative MR imaging in patients with breast cancer: Preoperative staging, effects on recurrence rates, and outcome analysis.* Magn Reson Imaging Clin N Am, 2006; 14(3):351-62, vi. doi: 10.1016/j.mric.2006.07.009.

19. Fischer U, Zachariae O, Baum F, Von Heyden D, Funke M, Liersch T: *The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer.* Eur Radiol, 2004, 14(10):1725-31. doi: 10.1007/s00330-004-2351-z.

20. Perrone A, Guerrisi P, Izzo L, D'Angeli I, Sassi S, Mele LL, Marini M, Mazza D, Marini M: Diffusion-weighted MRI in cervical lymph nodes: differentiation between benign and malignant lesions.

Eur J Radiol, 2011; 77(2):281-86. doi: 10.1016/j.ejrad.2009.07.039. Epub 2009 Aug 28.

21. Hata T, Takahashi H, Watanabe K, et al.: *Magnetic resonance imaging for preoperative evaluation of breast cancer: A comparative study with mammography and ultrasonography.* J Am Coll Surg, 2004, 199:173-74. DOI: 10.1016/j.jamcollsurg.2004.03.016.

22. Heywang-Köbrunner SH, Bick U, Bradley WG Jr, Boné B, Casselman J, Coulthard A, Fischer U, Müller-Schimpfle M, Oellinger H, Patt R, Teubner J, Friedrich M, Newstead G, Holland R, Schauer A, Sickles EA, Tabar L, Waisman J, Wernecke KD: *International investigation of breast MRI: results of a multicentre study* (11 sites) concerning diagnostic parameters for contrast-enhanced MRI based on 519 histopathologically correlated lesions. Eur Radiol, 2001; 11:531-46.

23. Hlawatsch A, Teifke A, Schmidt M, Thelen M: *Preoperative assessment of breast cancer: Sonography versus MR imaging.* AJR Am J Roentgenol, 2002; 179:1493-501. DOI: 10.2214/ajr.179.6. 1791493.

24. Holland R, Veling SH, Mravunac M, Hendriks JH: *Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery.* Cancer 1985; 56(5):979-90. DOI: 10.1002/1097-0142(19850901)56:5<979::aid-cncr2820560502> 3.0.co;2-n.

25. Houssami N, Hayes DF: Review of preoperative magnetic resonance imaging (MRI) in breast cancer: should MRI be performed on all women with newly diagnosed, early stage breast cancer? Cancer J Clin, 2009; 59(5):290-302. DOI: 10.3322/caac.20028.

26. Hwang ES, Kinkel K, Esserman LJ, Lu Y, Weidner N, Hylton NM: Magnetic resonance imaging in patients diagnosed with ductal carcinoma-in-situ: value in the diagnosis of residual disease, occult invasion, and multicentricity. Ann Surg Oncol, 2003.

27. Jatoi I, Proschan MA: Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: A pooled analysis of updated results. Am J Clin Oncol, 2005; 28:289-94.

28. Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, Manoliu RA, Kok T, Peterse H, Tilanus-Linthorst MM, Muller SH, Meijer S, Oosterwijk JC, Beex LV, Tollenaar RA, de Koning HJ, Rutgers EJ, Klijn JG: *Magnetic resonance imaging screening study group. efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition.* N Engl J Med, 2004; 351(5):427-37. DOI: 10.1056/NEJMoa031759.

29. Kristoffersen Wiberg M, Aspelin P, Sylvan M, Bone' B: Comparison of lesion size estimated by dynamic MR imaging, mammography, and histopathology in breast neoplasms. Eur Radiol, 2003; 13(6):1207-212. DOI: 10.1007/s00330-002-1718-2.

30. Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, Kuhn W, Schild HH: *MRI for diagnosis of pure ductal carcinoma in situ: A prospective observational study.* Lancet. 2007; 370:485-92. DOI: 10.1016/S0140-6736(07)61232-X.

31. Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, Kuhn W, Schild HH: *Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer.* J Clin Oncol 2005; 23(33):8469-476. DOI: 10.1200/JCO.2004.00.4960.

32. Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans

DG, Gilbert FJ, Griebsch I, Hoff RJ, Kessar P, Lakhani SR, Moss SM, Nerurkar A, Padhani AR, Pointon LJ, Thompson D, Warren RM: *MARIBS study group:Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: A prospective multicentre cohort study (MARIBS).* Lancet, 2005; 365(9473):1769-778. DOI: 10.1016/S0140-6736(05)66481-1.

33. Lehman CD, Gatsonis C, Kuhl CK, et al.: ACRIN *Trial 6667 Investigators Group: MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer.* N Engl J Med, 2007; 356:1295-303. DOI: 10.1056/NEJMoa065447.

34. Liberman L, Morris EA, Dershaw DD, Abramson AF, Tan LK: *MR imaging of the ipsilateral breast in women with percutaneously proven breast cancer.* Am J Roentgenol, 2003; 180(4):901-10. DOI: 10.2214/ajr.180.4.1800901.

35. Liberman L, Morris EA, Kim CM, Kaplan JB, Abramson AF, Menell JH, Van Zee KJ, Dershaw DD: *MR imaging findings in the contralateral breast of women with recently diagnosed breast cancer.* AJR, 2003; 180:333-41. DOI: 10.2214/ajr.180.2.1800333.

36. Linda A, Zuiani C, Londero V, Bazzocchi M: Outcome of initially only magnetic resonance mammography-detected findings with and without correlate at second-look sonography: Distribution according to patient history of breast cancer and lesion size. Breast, 2008; 17(1):51-7. DOI: 10.1016/j.breast.2007.06.004.

37. Malmartel A, Tron A, Caulliez S: Accuracy of clinical breast examination's abnormalities for breast cancer screening: Cross-sectional study. Eur J Obstet Gynecol Reprod Biol, 2019; 237:1-6. DOI: 10.1016/j.ejogrb.2019.04.003.

38. Mann RM, Loo CE, Wobbes T, Bult P, Barentsz JO, Gilhuijs KG, Boetes C: *The impact of preoperative breast MRI on the re-excision rate in invasive lobular carcinoma of the breast.* Breast Cancer Res Treat, 2010; 119(2):415-22. DOI: 10.1007/s10549-009-0616-6.

39. May M, Chin C2, Hirji S, Horowitz D, Bansil H, Feldman S, Ha R5, Connolly EP: *Comparing preoperative imaging modalities in patient selection for breast intraoperative radiotherapy*. J Surg Oncol, 2018; 118(6):959-65. doi: 10.1002/jso.25235. Epub 2018 Sep 27.

40. McCormack VA, dos Santos Silva I: *Breast density and parenchymal patterns as markers of breast cancer risk: A meta-analysis.* Cancer Cancer Epidemiol Biomarkers Prev, 2006; 15(6):1159-69. DOI: 10.1158/1055-9965.EPI-06-0034.

41. Menell JH, Morris EA, Dershaw DD, et al.: *Determination of the presence and extent of pure ductal carcinoma in situ by mammo-graphy and magnetic resonance imaging.* Breast J, 2005; 11:382-90.

42. Neubauer H, Li M, Kuehne-Heid R, et al.: *High grade and nonhigh grade ductal carcinoma in situ on dynamic MR mammo-graphy: characteristic findings for signal increase and morphological pattern of enhancement.* Br J Radiol, 2003; 76:3-12. DOI: 10.1259/bjr/14883856.

43. Olivas-Maguregui S, Villaseñor-Navarro Y, Ferrari-Carballo T, Morales-Chairez V, Michel-Ortega RM, Cerón-Lizarraga T, Silva-Godínez JC, Arrieta O: Importance of the preoperative evaluation of multifocal and multicentric breast cancer with magnetic resonance imaging in women with dense parenchyma. Rev Invest Clin, 2008; 60(5):382-89.

44. Orel S, Schnall M: *MR imaging of the breast for the detection, diagnosis and staging of breast cancer.* Radiology, 2001; 220:13-30. doi: 10.1148/radiology.220.1.r01jl3113.

45. Peters NH, Borel Rinkes IH, Zuithoff NP, Mali WP, Moons KG, Peeters PH: *Meta-Analysis of MR imaging in the diagnosis of breast lesions*. Radiology, 2008; 246(1):116-124. DOI: 10.1148/radiol.2461061298.

46. Pettit K, Swatske ME, Gao F, Salavaggione L, Gillanders WE, Aft RL, Monsees BS, Eberlein TJ, Margenthaler JA: *The impact of breast MRI on surgical decision-making: Are patients at risk for mastec-tomy?* J Surg Oncol, 2009; 100(7):5535-8. DOI: 10.1002/jso. 21406.

47. Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M: *Digital Mammographic Imaging Screening Trial (DMI-ST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening.* N Engl J Med, 2005; 353(17):1773-783. DOI: 10.1056/NEJMoa052911.

48. Pop CF, Stanciu-Pop C, Drisis S, Radermeker M, Vandemerckt C, Noterman D, Moreau M, Larsimont D, Nogaret JM, Veys I: *The impact of breast MRI workup on tumor size assessment and surgical planning in patients with early breast cancer.* Breast J. 2018; 24(6):927-33. doi: 10.1111/tbj.13104. Epub 2018 Aug 3.

49. Potente G, Messineo D, Maggi C, Savelli S: Practical application of contrast-enhanced magnetic resonance mammography [CE-MRM] by an algorithm combining morphological and enhancement patterns. Comput Med Imaging Graph, 2009; 33(2):83-90. Doi: 10.1016/j.compmedimag.2008.10.004. Epub 2008 Dec 17.

50. Sardanelli F, Bacigalupo L, Carbonaro L, Esseridou A, Giuseppetti GM, Panizza P, Lattanzio V, Del Maschio A: *What is the sensitivity of mammography and dynamic MR imaging for DCIS if the whole-breast histopathology is used as a reference standard?* Radiol Med, 2008; 113(3):439-51. doi: 10.1007/s11547-008-0250-0. Epub 2008 Jul 9.

51. Sardanelli F, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, Helbich T, Heywang-Köbrunner SH, Kaiser WA, Kerin MJ, Mansel RE, Marotti L, Martincich L, Mauriac L, Meijers-Heijboer H, Orecchia R, Panizza P, Ponti A, Purushotham AD, Regitnig P, Del Turco MR, Thibault F, Wilson R: *Magnetic resonance imaging of the breast: Recommendations from the EUSOMA working group.* Eur J Cancer, 2010; 46(8):1296-316. doi: 10.1016/j.ejca.2010.02.015. Epub 2010 Mar 19.

52. Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, Lattanzio V, Del Maschio A: Italian Trial for Breast MR in Multifocal/Multicentric Cancer: Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric logic examination as a gold standard. AJR Am J Roentgenol, 2004; 183(4):1149-157. doi: 10.2214/ajr.183.4.1831149.

53. Schelfout K, Van Goethem M, Kersschot E, Colpaert C, Schelfhout AM, Leyman P, Verslegers I, Biltjes I, Van Den Haute J, Gillardin JP, Tjalma W, Van Der Auwera JC, Buytaert P, De Schepper A: *Contrast-enhanced MR imaging of breast lesions and effect on treatment.* Eur J Surg Oncol, 2004; 30(5):501-07. DOI: 10.1016/j.ejso.2004.02.003.

54. Schelling M, Gnirs J, Braun M, Busch R, Maurer S, Kuhn W, Schneider KT, Graeff H: *Optimized differential diagnosis of breast lesions by combined B-mode and color Doppler sonography.* Ultrasound Obstet Gynecol, 10(1):48-53. DOI: 10.1046/j.1469-0705.1997. 10010048.x.

55. Schnall MD, Blume J, Bluemke DA, Deangelis GA, Debruhl N, Harms S, Heywang-Köbrunner SH, Hylton N, Kuhl CK, Pisano ED, Causer P, Schnitt SJ, Smazal SF, Stelling CB, Lehman C, Weatherall PT, Gatsonis CA: *MRI detection of distinct incidental cancer in women with primary breast cancer studied in IBMC 6883.* J Surg Oncol, 2005; 92:32-8. DOI: 10.1002/jso.20381.

56. Taourel P, Hoquet-Devaux M, Curros-Doyon F, Merigeaud S, Prat X: *Does breast density have an impact on the indications for MRI*? J Radiol, 2008; 89(9 Pt 2):1187-195.

57. Tillmann G, Orel S, Schnall M, Schultz D, Tan J, Solin L, et al.: *Effect of breast magnetic resonance imaging on the clinical management of women with early stage breast carcinoma.* J Clin Oncol, 2002; 20(16):3413-423.

58. Vachon CM, Van Gils CH, Sellers TA, Ghosh K, Pruthi S, Brandt KR, Pankratz VS: *Mammographic density, breast cancer risk and risk prediction.* Breast Cancer Res, 2007; 9:217. DOI: 10.1186/bcr1829.

59. Vachon CM, van Gils CH, Sellers TA, Ghosh K, Pruthi S, Brandt KR, Pankratz VS: *Mammographic density, breast cancer risk and risk prediction.* Breast Cancer Res, 2007; 9(6):217. DOI: 10.1186/bcr1829.

60. Vaidya TP, Rastogi A, Thakur M, Kembhavi SA, Popat PB: *Updated BI-RADS-What the radiologist needs to know.* Poster to ECR, 2018; C-1965. doi:10.1594/ecr2018/C-1965.

61. Van Goethem M, Schelfout K, Dijckmans L, Van Der Auwera JC, Weyler J, Verslegers I, Biltjes I, De Schepper A: *MR mammo-graphy in the pre-operative staging of breast cancer in patients with dense breast tissue: Comparison with mammography and ultrasound.* Eur Radiol, 2004; 14:809-16. DOI: 10.1007/s00330-003-2146-7.

62. Van Goethem M, Verslegers I, Biltjes I, Hufkens G, Parizel PM: *Role of MRI of the breast in the evaluation of the symptomatic patient.* Curr Opin Obstet Gynecol, 2009; 21(1):74-9.

63. Warren R, Ciatto S, Macaskill P, Black R, Houssami N: *Technical aspects of breast MRI. Do they affect outcomes?* Eur Radiol, 2009; 19: 1629-638. DOI: 10.1007/s00330-009-1341-6.

64. Wood WC: *Close/positive margins after breast-conserving therapy: Additional resection or no resection?* Breast. 2013; 22 Suppl 2:S115-7. doi: 10.1016/j.breast.2013.07.022.

65. Yaffe MJ: *Mammographic density. Measurement of mammographic density.* Breast Cancer Res, 2008; 10(3):209. DOI: 10.1186/ bcr2102.

66. Yoon JH, Kim MJ, Lee HS, Kim SH, Youk JH, Jeong SH, Kim YM: Validation of the fifth edition BI-RADS ultrasound lexicon with comparison of fourth and fifth edition diagnostic performance using video clips. Ultrasonography, 2016; 35(4):318.