The impact of presurgical magnetic resonance in early breast cancer: an observational study

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Summary

The aim of this study was to evaluate the impact of presurgical breast magnetic resonance imaging (MRI) on the surgical management of selected patients with early-stage breast cancer who were candidates for BCT. The sample was built up according to the EUSOMA (European Society of Breast Cancer Specialists) recommendations enrolling women with unifocal unilateral early-stage breast carcinoma diagnosed by mammography, ultrasound (US) examination and in some cases also by histological analysis; all were scheduled for wider local excision. All eligible patients underwent presurgical breast MRI and findings were classified according to the BI-RADS system. In the presence of additional foci classified as BI-RADS 3-4, a targeted second-look US study was performed. If second-look US confirmed the presence of foci, needle biopsy was performed. Possible changes in the therapeutic approach resulting from preoperative MRI findings were decided upon by a multidisciplinary team. Outcome of histological examination of the surgical specimen and particularly analysis of tumor infiltration of the resection margins was the standard for determining the appropriateness of surgical strategy. A total of 123 patients underwent presurgical breast MRI. Additional foci were detected in 41.6% of patients, a greater local extension of the index lesion in 6.4%, whereas MRI confirmed local staging established by conventional imaging in 52%. However, 13.8% of additional foci were not confirmed by second-look and needle biopsy. More extensive surgery as a result of MRI findings was performed in 34.2%. This decision proved to be appropriate in 29.3% thus resulting in an over-treatment rate of 4.9%. Presurgical breast MRI resulted in confirmation of planned surgical strategy in 65.8% with an appropriateness rate of 54.5%. Surgical resection margins were positive for malignancy in 11.3% and repeated surgery was therefore required. Therapeutic strategy established on the basis of MRI was appropriate in 83.8% of cases. This study confirms the utility of MRI in presurgical workup of selected breast cancer patients. The results obtained suggest the importance of a sensitive tool such as MRI in the local staging of breast cancer before treatment planning.

Key words: Early-stage breast cancer; Breast magnetic resonance imaging; Presurgical staging.

Introduction

Breast conserving treatment (BCT), including wider local excision or quadrantectomy plus radiation therapy, 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 [1].

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, accurate local staging of breast cancer is essential (extent of index lesion, multifocality, multicentricity, contralateral cancer) [2, 3]. Various studies have demonstrated 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) [4-13], 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 false-negatives produced by mammography [14-16]. However, a significant number of multifocal and multicentric breast carcinomas are still missed at routine diagnostic imaging [17]. 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 [18].

According to international oncology guidelines [19] MRI as a staging procedure in women with breast cancer is optional, but according to EUSOMA (European Society of Breast Cancer Specialists) [20] 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 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.

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Materials and Methods

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 2009 to September 2011 at the Department of Radiological Sciences, University of Rome "Sapienza" among women with unilateral unifocal early breast cancer. Diagnosis was based on clinical examination, X-RM and 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 X-RM 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. US and Doppler US studies were performed by the same radiologist according to previously reported standards [21]. 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) 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 [22]: type A, the breast is almost entirely fat (glandular parenchyma < 25% of the total area of both breasts); type B, scattered fibroglandular densities (25%-50%); type C, heterogeneously dense breast tissue (51%-75%); type D extremely dense (> 75% glandular).

Before MRI, US guided needle biopsy of the index lesion was performed in some cases 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 ≤ 50), positive for BRCA1/2 gene mutations (subjects with a positive test for 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 one full-term pregnancy), lactation for at least three months (yes/no).

Patient population was selected according to the following inclusion criteria:

– mammography: elevated mammographic density (BI-RADS C or D), 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 ≤ 50 years with a clinical history positive for breast carcinoma);

– characteristics of the lesion and treatment plan: the study included only women with unilateral unifocal lesions smaller than 3 cm in diameter for whom the interdisciplinary medical team had indicated wider local excision on the basis of 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 1.5 T 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 a 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 [4]. Patients receiving hormone replacement therapy underwent MRI a minimum of four weeks after discontinuation of treatment [5].

The examination was carried out using a 1.5 T magnet (Avanto, Siemens Medical Solutions, Germany) equipped with bilateral multichannel dedicated coil with an integrated compression mechanism. The patient was positioned face down on a 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 so as to minimize any motion artifacts.

Morphological study was performed using T2-weighted short tau inversion recovery (STIR) unenhanced axial-plane 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°; matrix = 3.84 x 3.84 ; pixels = 1 x 1 x 1; field of view (FoV) = 380 x 380; slice thickness = 1 mm; interslice gap = 0.2 mm.

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

Contrast medium was gadoterate meglumine (Dotarem, Guerbet, France) 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 generation of percent enhancement versus time curves was performed through positioning of regions of interest (ROI) for all identified enhancing lesions with a diameter ≥ 5 mm and mass-like morphology according to the MRI BI-RADS classification [6].

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 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.

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) [7, 23]. All lesions were classified in one of the six BI-RADS categories according to their probability of being malignant [6].

Targeted second-look US 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 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 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.

Table 1. — *Main characteristics of the enrolled patients and indications for breast MRI.*

Variables	Sample (N = 123)
Age at cancer diagnosis (years; mean)	50.2 ± 10.4
Menopausal status (%)	
menopause	55.2%
Non 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 AB (non dense breast)	49.5%
BI-RADS CD (dense breast)	50.5%
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%

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

Results

The sample was selected from 374 patients with clinical, mammographic, US and in some cases 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 1.

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

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

– in 6.4% MRI showed 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 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%) (Figure 1), with unilateral mastectomy in 10.7% due to multicentricity (Figure 2) and with bilateral mastectomy in 3.2% due to bilaterality.

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

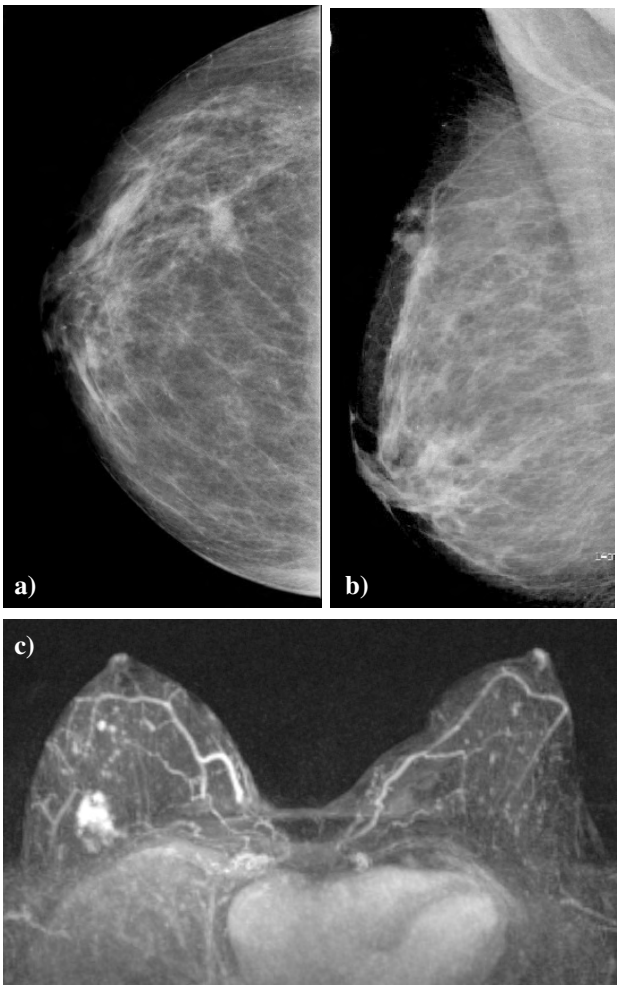

Figure 1. — A 67-year-old patient with an unifocal unilateral lesion detected at mammography (a, b) and US originally scheduled for wider local excision. MIP reconstructions of FL 3D DYN T1-weighted sequences (c): in addition to the index lesion in the upper outer quadrant of the right breast, more foci are evidenced in the same quadrant (BIRADS 5) leading to diagnosis of multifocal carcinoma. On the basis of MRI outcome, the multidisciplinary team performed quadrantectomy instead of wider local excision. Postoperative histological analysis confirmed the appropriateness of this change of surgical strategy.

– 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 findings 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%.

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 presurgical staging of patients with primary breast cancer is evolving [1, 24-26].

The value of breast MRI is based on the capability of this modality to depict: (a) multicentric and multifocal disease [27-30], (b) an invasive component in ductal carcinoma in situ lesions [31], (c) the tumor in a three-dimensional way [27, 32], and (d) cancer in dense breast tissue [33-35]. Thus, MRI has facilitated improved local staging (extent of index lesion, multifocality, multicentricity, contralateral cancer) [4-8] and safer breast-conserving surgery in patients with breast lesions, thereby reducing the risk of local recurrence [36, 37]. Furthermore, contrary to initial assumptions, MRI has also proved to be able to detect invasive lobular carcinoma and ductal carcinoma in situ (DCIS) as well as the extensive intraductal component that can appear as "non mass like" enhancement [31, 38-42].

Numerous studies have been performed to assess the diagnostic performance of MRI in the evaluation of breast lesions [43, 44]. 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 [45].

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 [7]. 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 [46]. In this study, MRI detected additional foci in 41.6% and more extensive surgery was performed in 34.2%. This decision proved appropriate in 29.3% with an overtreatment rate of 4.9%. 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 on the basis of risk factors such as mammographic features, family history of breast cancer and/or histological analysis as indicated in the EUSOMA recommendations [20]. In accordance with these recommendations, patients eligible for PBI on the basis of 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 find-

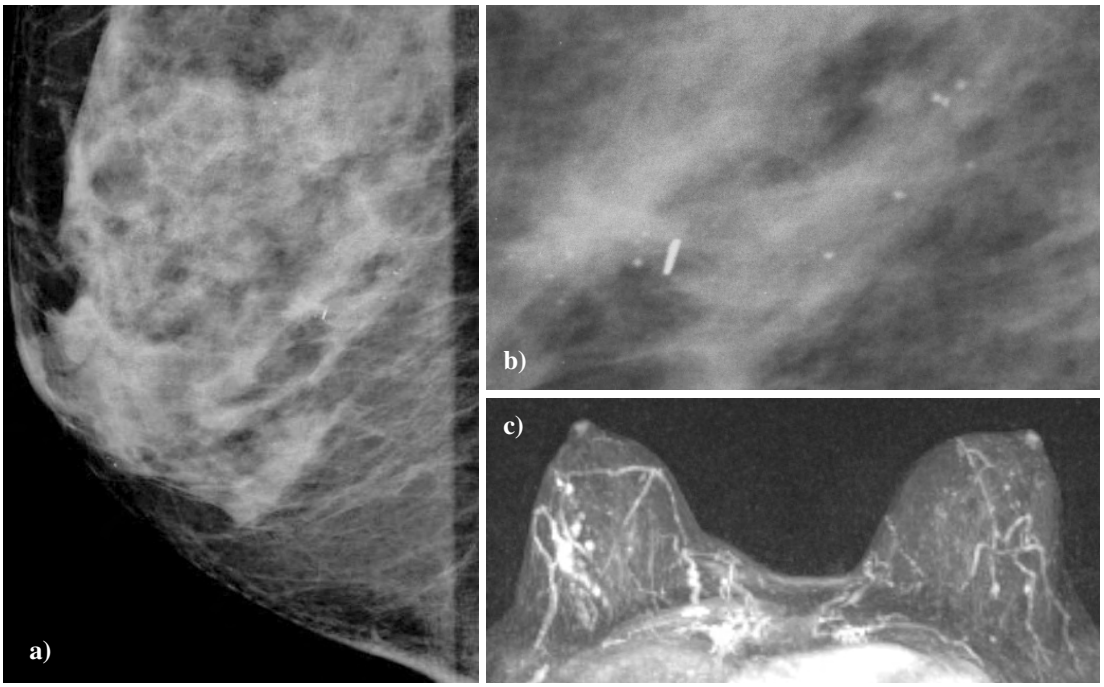

Figure 2. — A 54-year-old patient with high mammographic density (BI-RADS C) and suspicious micro calcifications detected at mammography (a, b) in the lower inner quadrant of the right breast. MIP reconstructions of FL 3D DYN T1-weighted sequences (c): in addition to the main lesion located in the lower 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 unilateral mastectomy. Postoperative histological analysis confirmed the appropriateness of this modified therapeutic strategy.

ings confirms the value of second-look US and needle biopsy of the additional lesions detected by MRI [47]. 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.

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 four weeks after discontinuation of hormone replacement therapy) were performed according to the EUSOMA recommendations, and a standardized method such as BI-RADS lexicon was employed for the interpretation. Furthermore, changes in therapeutic planning were decided on by a multidisciplinary team.

On the other hand, 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.

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 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 US as well as histological confirmation of additional foci detected by MRI.

Changes in therapeutic management resulting from preoperative MRI findings should be decided on by a multidisciplinary team.

Careful prospective randomized trials are required to determine whether MRI in the preoperative assessment of women with diagnosis of breast cancer leads to a decrease in tumor recurrence and to determine the cost-effectiveness of this approach.

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