Diplomarbeit

Predictive Value of Magnetic Resonance Imaging in Patients Classified as BI-RADS™ 1 to 3.

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Ort, Datum …….. (Unterschrift)

Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, August 25th 2010 *Claudio Spick*

Preface

Aus Gründen des raschen Wachstums, einer globalisierten Kommunikation in der Medizin und meiner persönlichen Entwicklung, habe ich mich dazu entschlossen meine Diplomarbeit in englischer Sprache zu verfassen.

Taking into consideration the rapid growth of international communication in medicine and my personal development I have opted to write my diploma thesis in English.

Since I started studying medicine, I have learned about the human body, its functions and diseases in detail. My interest for imaging and diagnosis grew permanently. Thus, I decided to write my thesis about this topic in particular exploring the predictive value of breast magnetic resonance imaging.

Acknowledgements

I would like to thank all the people who supported me in writing this thesis.

In particular I want to express my most sincere appreciation to Dieter Szolar who as my mentor guided me and gave me the opportunity to write my thesis at the Diagnostikum Graz Sued West.

I would also like to thank Helmut Schöllnast for his assistance as supervising tutor.

A special thanks to my family, in particular my parents and my brother, not only for giving me the opportunity to study medicine, but also for supporting me in all of my endeavors. It was your love and encouragement that helped me through this process. I am eternally grateful.

Zusammenfassung

Negativer Vorhersagewert der MR-Mammographie (MRM) bei Läsionen mit der MRM BI-RADS™ Klassifikation 1-3.

Ziel. Die kontrastmittelverstärkte Magnetresonanz Mammographie (MRM) wurde in den 80er Jahren in die klinische Routine eingeführt und hat seither einen wichtigen Stellenwert bei der radiologischen Abklärung von Brusterkrankungen erhalten. Sie ist die sensitivste Ergänzung zur Röntgen-Mammographie und wird unter anderem als Problemlösungsmethode bei inkonklusiven Vorbefunden verwendet.

2003 wurde die erste Version des Breast Imaging Reporting and Data System (BI-RADS®) für MRM von dem American College of Radiology (ACR) veröffentlicht. Mit dem Ziel, die Interpretationskriterien der Brustläsionen zu standardisieren, sollte sowohl die Kommunikation zwischen Radiologen als auch der interdisziplinäre Therapie- und Kontrollverlauf der Patienten erleichtert werden. Außerdem wurde durch das Lexikon mit Beschreibung über Morphologie und funktionellen Parameter die Spezifität der MRM wesentlich erhöht.

Bis heute gibt es nur wenige und vor allem limitierte Studien, welche die Malignitätsrate bei benignen (MRM BI-RADS 2), sowie wahrscheinlich benignen (MRM BI-RADS 3) Brustläsionen evaluieren.

Ziel ist die Bestimmung des negativen Vorhersagewertes der MRM in Bezug auf Läsionen, die mit der MRM als BI-RADS 1-3 Läsionen klassifiziert wurden.

Die Bedeutung ergibt sich aus der Evaluierung der Vergleichbarkeit des etablierten mammographischen BIRADS Systems mit dem MRM-BIRADS System.

Zielgröße ist die Häufigkeit von malignen Läsionen nach benignem MRM Erstbefund innerhalb eines Zeitintervalls von mindestens 2 Jahren.

Material und Methoden. In dieser Studie wurden 1237 Befunde von Patientinnen, bei denen im Zeitraum 2000 bis 2007 eine MRM durchgeführt wurde, retrospektiv ausgewertet.

Evaluiert wurde die Entwicklung aus dem Erstbefund in der MRM aufgrund der Krankengeschichte unter Einbeziehung von MRM Verlaufskontrollen, histologischen Befunden nach Stanzbiopsien und/oder Operationen sowie klinischem Verlauf. Die dementsprechende Datenerhebung erfolgte aus OP-Berichten, Arztbriefen und pathologischen Befunden.

Die Patientinnen wurden über einen Zeitraum von mindestens 2 Jahren verfolgt. (Intervall 2-9 Jahre).

Resultate. 740 Patientinnen konnten in die Studie eingeschlossen werden. 248 Patientinnen mit adäquaten Daten und Beobachtungsintervall wurden evaluiert. Histopathologisch wurden 149 Läsionen als benigne und 15 Läsionen als maligne klassifiziert. Die verbleibenden 84 Patientinnen ohne histopathologischem Befund, wiesen keine signifikanten Veränderungen während der Beobachtungszeit auf und wurden daher als benigne klassifiziert.

Der negative Vorhersagewert der MRM bei Brustläsionen klassifiziert mit BI-RADS 1-3, betrug 93.9%. Eine weitere Analyse beschreibt, dass keine Patientin (0.0%) mit MRM BI-RADS 1, 4 Patienteninnen (1.6 %) mit MRM BI-RADS 2 und 11 Patientinnen (4.4 %) mit MRM BI-RADS 3 eine maligne Läsion innerhalb des beobachteten Zeitintervalls (2-9 Jahre) entwickelten.

Konklusion. Die MRM besitzt einen hohen negativen Vorhersagewert. Brustläsionen die als wahrscheinlich benigne klassifiziert wurden (MRM BI-RADS 3) entwickelten häufiger Malignität als Brustläsion klassifiziert mit BI-RADS 1 und BI-RADS 2. Eine weitere Entwicklung der BI-RADS 3 Klassifikation wird erwartet.

Abstract

Predictive Value of Magnetic Resonance Imaging in Patients Classified as BI-RADS™ 1 to 3.

Purpose. The aim of this study was to evaluate the negative predictive value (NPV) of magnetic resonance mammography (MRM) in patients classified as MRM BI-RADS 1-3.

Methods and Materials. In this single center study, we retrospectively analyzed 1237 patients (mean age, 50±13 years; range 18-89 years) who underwent MRM between May 2000 and May 2007.

The initial MRM findings were matched with the follow-up information derived by histopathology and mammography and/or MRM. Patients were followed over a time interval of at least 2 years (range, 2-9 years).

Results. 740 patients were included in this analysis. 248 patients who had MRM examinations classified as BI-RADS 1-3 and who had adequate follow-up were analyzed. In histopathology, 149 lesions were classified as benign and 15 lesions were classified as malignant. The remaining 84 patients without histopathologic evaluation of the breast lesion did not exhibit significant changes in symptoms or imaging findings during the follow-up period and were therefore classified as benign. The NPV of MRM in lesions classified as BI-RADS 1-3 was 93.9%. A subgroup analysis revealed that no patient (0.0%) with MRM BI-RADS 1, 4 patients (1.6%) with MRM BI-RADS 2, and 11 patients (4.4%) with MRM BI-RADS 3 developed a malignant breast lesion.

Conclusion. MRM shows a high NPV in patients classified as BI-RADS 1-3. Lesions classified by MRM as probably benign showed a higher frequency of developing malignant disease compared to lesions classified as BI-RADS 1-2.

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1 Introduction

1.1 Breast Cancer

Breast carcinoma is the most frequent malignant disease among women in the world. According to the International Agency for Research on Cancer (IARC), there are approximately 1.2 million new diagnoses of worldwide breast carcinoma every year, 410.000 are followed with death (1). One in eight women will be diagnosed with cancer of the breast during their lifetime(2).

The incidence shows major geographically differences. Unlike developing countries, such as countries from sub Saharan-Africa or China, which have the lowest number (less than 20/100.000) of new cases diagnosed with breast cancer, the highest rates (80-90/100.00) are found in North America, Europe, Australia, South America, including Brazil and Argentina. (Figure 1)

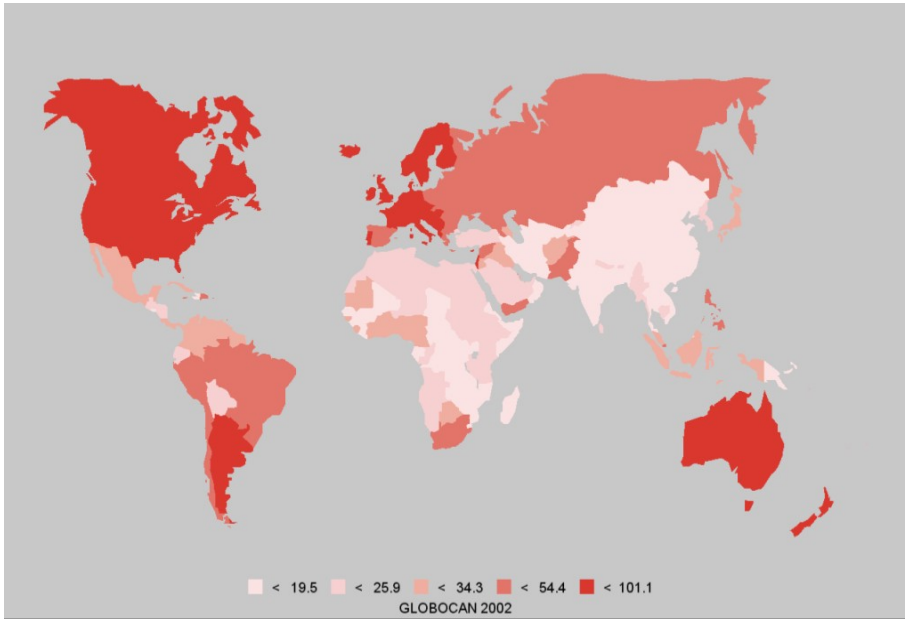

Figure 1. Incidence of Breast cancer: World - All Ages (1)

Survival from breast cancer has steadily increased in developed countries, where it now achieves 85%, following improvements in early detection and treatments. On the other hand, survival in developing countries remains around 50-60%. The applications of adjuvant chemotherapy and hormone treatment have mainly improved the relapse-free and overall survival. Nevertheless, recurrence and death as a result of disseminated disease remains high. Therefore it is apparent that more effective strategies for the prevention and treatment of this malignancy are urgently needed.

1.2. Histopathology

The majority of the neoplasms of the breast develop from the ductal epithelium, while a minority originates from the lobular epithelium, whereas ductal carcinomas have been recently increasing. In consideration of prognosis and histology the World Health Organization (WHO) classified difference subtypes of breast cancer (3). The subdivision includes non-invasive carcinomas, invasive carcinomas and morbus Paget. Non-invasive carcinomas contain ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Invasive Carcinomas are subdivided in ductal, lobular, lobular-ductal, mucinous, medullary, tubular, papillary, cribriform and neuroendocrine types.

Breast carcinoma is a systemic disease where cancer cells may start to be disseminated into blood and lymphatic systems even in early stages. Critical angiogenesis may occur in breast tumor nodules as small as 2 mm in

diameter and each gram of tumor leads to diffuse around 100 cells per day into blood vessels, in state of metastasis.

1.3. Risk Factors

The hormone estrogen captures a major role in the carcinoma development of the breast. Increased proliferation of cancer cells is the result of the expression of peptide growth factor, induced by estrogen binding to the estrogen receptor. In fact, the majority of women, namely 60% - 75% premenopausal and postmenopausal, respectively, have estrogen dependent carcinomas. Therefore, it is expected that anti-estrogen selective receptor modulators will show reduced risk of breast cancer. However, especially the combination of estrogen and progesterone increases breast cancer risk (4). Nevertheless, there remains a critical need to develop agents for estrogen receptor-negative breast cancer with reduced toxicity and increased efficacy.

Risk factors are virtually in every type of cancer well established. There are many relative risks for developing breast cancer [Table 1]. Relative risk is calculated based on the comparison of the incidence of breast cancer or its related death in women with a specified risk factor against those women without such factor. This helps to determine risk factors that might cause breast cancer. However, it has been shown that 70% of all women with breast cancer have no known risk factors. A remaining problem is the lack of preventive measurements. Therefore, early detection and treatment are considered the most promising approach to reduce breast cancer mortality.

Table 1. Risk Factors (5)

Relative Risk	Factor
HIGH >4.0	• Female • Age (> 65 versus < 65 years, although risk increases across all ages until age 80) • Certain inherited genetic mutations for breast cancer (BRCA 1 and/or BRCA 2) • Two or more first degree relatives with breast cancer diagnosed at an early age • Personal history of breast cancer • High breast tissue density • Biopsy confirmed atypical hyperplasia
MIDDLE 2.1-4.0	• One first degree relative with breast cancer • High-dose radiation to chest • High bone density (postmenopausal)
LOW 1.1-2.0	• Late age at first full-term pregnancy (>30 years) • Early menarche (<12 years) • Late menopause (>55 years) • No full term pregnancies • Never breastfeed a child • Recent oral contraceptive use • Recent and long-term hormone replacement therapy

	• Obesity (postmenopausal) • Personally history of endometrium, ovary or colon cancer • Alcohol consumption • Height • High socioeconomic status • Jewish heritage

1.4. Detection

1.4.1. Clinical Breast Examination

The clinical examination of the breast and its lymph channels should be an integral part of any screening procedure and any diagnostic mammography (6).

Correct performance should include the inspection and palpation of the entire breast. Additionally, palpable lymph nodes of the cervical, axillary and supraclavicular area have to be assessed.

A palpable lump has to be documented in its size, its texture, its contour, surrounding tissue, depth extension, signs of swelling or redness, fixation to the skin and surface, as well as the nipple retraction. Despite monthly breast self-examination is frequently recommended, evidence for its effectiveness is weak (7, 8).

1.4.2. Mammography

Mammography is currently the most effective method for the detection of breast cancer and early tumor stages of the breast (6). No other type of cancer shows impact and effectiveness of a screening method evaluated and documented as well as for breast cancer and its detection by mammography (6). The implementation of a mammogram has to meet the guidelines on quality assurance and mammography Quality Standards Act (9). After ensuring the investigations technical conditions, a systematic and reproducible analysis of the images for abnormalities can be conducted. To meet the requirements of quality, a standardized mammography should have standardized interpretation according to the Breast Imaging Reporting And Data System (BI-RADS) classification of the American College of Radiology (32).

Mammography is performed using ionizing radiation to image breast tissue. During the examination the breast is compressed firmly between a plastic plate and a x-ray cassette that contains a special x-ray film or a digital detector system, respectively. A standard mammogram is taken in mediolateral oblique and craniocaudal projections. Images obtain details of the composition, structure and type of glandular tissue of the breast.

Indications for mammography are discomfort in the breast or suspicious findings in palpation. Furthermore, it is indicated in knots, lumps, resistant pain or skin thickening.

Exceptions for the significance of mammography are cysts in young women (<40 years) diagnosed with ultrasound. Further indications where mammography is the most important diagnostic method are the non-puerperal mastitis as a differential diagnosis of inflammatory breast cancer, the pathological secretion of the breast and clarification of prominent lymph nodes.

Aside diagnostic mammograms with specific indications, screening mammography applied in asymptomatic woman has to be distinguished. Screening mammography has shown to be the most precise modality that can improve the prognosis of breast cancer, due to early detection and recognition of small tumors. Early detection of breast cancer is the most effective possibility to reduce mortality.

Mammography shows an overall sensitivity in detection of breast cancer of approximately 79%. It is lower in younger women and in those with dense breast tissue. Overall specificity is approximately 90% and is also lower in younger women and in those with dense breasts. The rate of cancer not detected by mammography is 5-15% (10). In addition to the density of the breast's parenchyma, also the characteristics of the tumor itself and the insufficient experience of the investigator or inadequate X-ray technology may be a limitation for the detection of cancer.

Several studies have demonstrated that screening mammography and its early detection of breast cancer is the most effective method to reduce mortality (11) (12) (13). The HIP study has shown a reduction of mortality by

40% for women with an age>50 years and the Östergötlandstudie has proven a reduction of 31% for women with an age of 40-74 years (14) (15).

Another advantage of screening mammography lies in the improvement of breast-conserving therapy associated with a decrease in ablation. Breast carcinomas detected with screening are in average less than half the diameter than the carcinomas of patients without screening, as demonstrated by the Stockholm trial (16). Moreover, an increase of detected ductal carcinoma in situ has been achieved, which may develop into an invasive carcinoma.

The risks of mammography resulting from radiation exposure should not be entirely ignored. Due to the low-dose the risk of radiation-induced breast cancer remains vanishingly small and can only be calculated theoretically. The risk is about 0.01% compared to the approximate ten percent risk for women to develop breast cancer disease. After 40 years of age the individual benefits of mammography begins to outweigh the radiation risk. The optimum ratio of benefits vs. risk is achieved between the 50 and 70 years of age (6).

Early detection of breast carcinoma is one of the most promising tactics to achieve better prognosis and lower rate of death. Randomized screening trials with mammography result in 15–20% reduction in the risk of death related to breast cancer (17-19). Detection of breast cancer before it becomes palpable is a premise for breast cancer screening. High-quality follow-up and successful treatment is the benefit of early diagnosis. Therefore, the American Cancer Society (ACS) promotes its guidelines for mammography screening [Table 2].

Table 2. Screening Guidelines For the Early Detection of Cancer in Asymptomatic People (20)

Breast	Recommendation
	• Yearly mammograms are recommended starting at age 40. The age at which screening should be stopped should be individualized by considering the potential risks and benefits of screening in the context of overall health status and longevity.
	• Clinical breast exam should be part of a periodic health exam about every 3 years for women in their 20s and 30s and every year for women 40 and older.
	• Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-exam is an option for women starting in their 20s.
	• Screening MRI is recommended for women with an approximately 20% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease.

1.4.3. Ultrasound

In recent years, ultrasound has emerged to one of the most important additive imaging methods in breast diagnostics for evaluation of palpable findings, unclear mammographic densities and diagnosis of cysts (6). The aim of each examination is to investigate the entire breast and a five level classification based on the BI-RADS classification should document final findings and recommend further procedure.

Ultrasound serves to differentiate cysts from solid lesions. In addition, ultrasound can also be used if focal lesions are superimposed by dense parenchyma in mammography. A key role of ultrasound is to determine the localization of a palpable lesion if the mammogram has been indecisive. For initial evaluation of the breast ultrasound should be the first imaging modality in younger patients in whom occurrence of a malignancy is very unlikely, in pregnant women and for women during lactation. Despite the use of high-resolution ultrasound the ultrasound detection of circumscribed microcalcifications can be missed out entirely. However, breast ultrasound may be helpful in the analysis of the surrounding parenchyma of microcalcifications. By detecting suspicious foci it may give additional evidence of the extent of the process. Finally, ultrasound is very useful in the support of interventional techniques that require ultrasound control, such as minimal invasive diagnostic (core biopsy, vacuum biopsy) or preoperative localization and fine needle aspiration biopsy.

1.5. Magnetic Resonance Imaging

Magnetic resonance (MR) imaging applies magnetic fields to produce detailed cross-sectional images of tissue structures. The body is largely composed of water molecules, thus the magnetic moments of hydrogen atoms align with the direction of the magnetic field produced from MRI. After alteration of the magnetic field, alignment changes create a signal that can be detected by the scanner. The return to equilibrium of the water protons is characterized by the T1 and T2 relaxation times, after receiving radiofrequency (RF) through an external source, the RF coil.

Breast MRI (MR mammography, MRM) utilizes a T1-weighted technique that is sensitive to the accumulation of gadolinium-based contrast agents. These contrast agents are injected intravenously to provide reliable detection of lesions, and act to shorten T1 and increase signal intensity. Thus, an early (within 2 min), and significant signal increase reflects a higher density and/or higher leakiness of microvessels, which can be a reflection of tumor angiogenesis. Although, breast malignancies show a signal enhancement, not all signal enhancements represent cancer, leading to the high sensitivity, but low-to-moderate specificity of breast MRI.

Contrast between tissues in the breast depends on the mobility and the magnetic environment of the hydrogen. Water and fat contribute to the signal that determines the brightness of tissues in the image. This results in images showing predominantly parenchyma and fat and lesions if they are present. Lesions can be detected because the protons in different tissues return to

their equilibrium state at different rates. By changing the parameters on the scanner this effect is used to create contrast between tissues.

Contrast-enhanced MRM was first performed in the late 1980s in women with biopsy proven carcinomas (28). It has been shown that breast carcinomas show significant enhancement following application of contrast agents. To differentiate the different tissues a threshold for significant enhancement was used. However, further studies have investigated that not only malignant but also benign lesions may show a similar enhancement. Thus distinguishing between malignant and benign lesions still remains a challenge.

To improve the specificity of MRI two different concepts have been developed. The first concentrates on high spatial resolution to investigate the morphologic characteristics, and the second focuses on temporal resolution to investigate the enhancement pattern. Previously, a technology which analysis both features simultaneously has not been available (29). Advanced methods, such as parallel imaging, use multiple received coil elements to encode spatial information in addition to traditional gradient encoding. Thus, parallel imaging has allowed optimization of both spatial and temporal resolution, in order to improve assessment of breast lesions. The ACR has published the recommended indications for breast MR imaging [Table 3].

Table 3. Indications for Breast MR imaging according to the American College of Radiology

• Equivocal findings at mammography and ultrasound
• Lesion characterization
• Neoadjuvant chemotherapy

- Infiltrating lobular carcinoma
- Infiltrating ductal carcinoma
- Axillary adenopathy, primary unknown
- Postoperative tissue reconstruction
- Silicone and non silicone breast augmentation
- Invasion deep to fascia
- Contralateral breast examination in patients with breast
- malignancy
- Post lumpectomy for residual disease
- Surveillance of high-risk patients
- Recurrence of breast cancer

There is a rapid progress in the field of breast MR imaging and several new techniques are looking forward to improve its appliance and diagnostic accuracy in the future.

MR imaging scanners with higher field strengths of 3.0 T have shown advantages in higher spatial resolution compared to 1.5 T MR imaging. One study has revealed a significant improvement in differential diagnosis of enhancing breast lesions at 3.0 T in the same patients, who have also been evaluated with 1.5 T MRI (30). Nevertheless, 3.0 T imaging acquisition needs further evaluation because T1 relaxation times at higher field strengths may affect the visibility of lesions on contrast enhanced images.

In adjunction to conventional contrast-enhanced MR imaging techniques further functional MRI sequences such as diffusion weighted imaging and MR spectroscopy can provide in vivo measurements of tissue microstructure and metabolism.

Diffusion weighted (DW) imaging is more sensitive to biophysical characteristics such as cell density, membrane integrity, and microstructure, respectively. It has been shown that DW imaging of the breast demonstrates decreased diffusion in malignant lesions, presumed to reflect increased cell density associated with breast tumors (53). Additionally, increases in diffusion coefficients of malignant lesions in response to treatment are earlier than changes in tumor size or vascularity (54).

MR spectroscopy (MRS) uses the small differences in the magnetic field in different chemical compounds to measure their concentrations in tissue. Especially the cell membrane marker choline has shown elevated levels in breast malignancies and therefore has improved the specificity of breast MRI (31).

Although mammography has shown early detection of breast cancer leading to reduction of mortality, there is less sensitivity for woman at increased risk of breast cancer and in woman under the age of 40 particularly. Therefore other screening strategies, such as earlier initiation of screening, shorter screening intervals or the addition of screening modalities, particularly magnetic resonance imaging, may be more useful in patients with increased risk. Thus, the ACS has published its recommendations also for breast MRI screening as an adjunct to mammography [Table 4]. Screening studies, using MRI in woman at higher risk, have reported significantly higher sensitivity for MRI compared with mammography or any of the other modalities, although specificity was more variable. (21-27)

Table 4. Recommendations for Breast MRI screening as an Adjunct to Mammography

Breast	Recommendation
	• Recommend Annual MRI Screening (Based on Evidence*) - *BRCA*-mutation - First-degree relative of *BRCA*-carrier, but untested - Lifetime risk ~20–25% or greater, as defined by BRCA or other models that are largely dependent on family history
	• Recommend Annual MRI Screening (Based on Expert Consensus Opinion†) - Radiation to chest between age 10 and 30 years - Li-Fraumeni syndrome and first-degree relatives - Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
	• Insufficient Evidence to Recommend for or Against MRI Screening‡ - Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history - Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH) - Atypical ductal hyperplasia (ADH) - Heterogeneously or extremely dense breast on mammography - Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)
	• Recommend Against MRI Screening (Based on Expert Consensus Opinion) • Women at □15% lifetime risk

*Evidence from nonrandomized screening trials and observational studies.
†Based on evidence of lifetime risk for breast cancer.
‡Payment should not be a barrier. Screening decisions should be made on a case-by-case basis, as there may be particular factors to support MRI. More data on these groups is expected to be published soon.

1.6. Breast Imaging Reporting and Data System

Breast magnetic resonance (MR) imaging (magnetic resonance mammography, MRM) has gained high importance for the detection and characterization of breast lesions. The first edition of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS®) has been published in 2003 (32), reproducing the significance of this imaging technique. A multimodal classification system has been developed for breast MRI lesions considering both, morphology and dynamics of contrast enhancement (33)-(34).

The approach to BI-RADS® was to establish standard interpretation criteria. Therefore, optimized evaluation of breast MRI studies with its different enhancement and morphological patterns is essential. By analyzing both, the morphology and kinetic behavior of a lesion, the specificity of breast MRI is improved. Thus, the BI-RADS classification focuses in describing both architectural features and dynamic parameters. This standardized lexicon for analysis of findings determined in breast MRI improves on one hand the communication between radiologist and referring physicians and on the other hand it allows analysis of outcomes across institutions to validate management recommendations.

The ACR established a consensus in terms of the different findings seen in breast MRI [Table 5].

Table 5. Breast MR imaging Terms Proposed by the International Working Group of the American College of Radiology

- Focus/foci
- Mass margin
  - Smooth
  - Irregular
  - Spiculated
- Mass shape
  - Round
  - Oval
  - Lobular
  - Irregular
- Mass enhancement
  - Homogeneous
  - Heterogeneous
  - Rim
  - Dark internal septation
  - Enhancing internal septations
  - Central enhancement
- NonMass enhancement
  - Focal
  - Linear
  - Ductal
  - Segmental
  - Regional
  - Multiple regions
  - Diffuse
- NonMass enhancement descriptors for all
  - other types
  - Homogeneous
  - Heterogeneous
  - Stippled/punctate
  - Clumped
  - Reticular/dendritic
- Symmetric versus asymmetric for bilateral studies
- Other findings
  - Nipple retraction
  - Nipple invasion
  - Precontrast high duct signal
  - Focal skin thickening
  - Diffuse skin thickening
  - Skin invasion
  - Edema
  - Lymphadenopaty
  - Pectoralis muscle invasion
  - Chest wall invasion
  - Hematoma/blood
  - Abnormal signal void Cysts

Kinetic enhancements are particularly helpful if the characterized breast lesion has benign morphologic features. On the one hand, any suspicious morphologic finding should be biopsied immediately while kinetic behavior is less important, but on the other hand if the lesion appears to be a well-defined benign mass the kinetic features support the decision for biopsy or follow-up of the lesion. For kinetic analysis it is required to use high temporal resolution to acquire multiple data after administration of intravenous contrast material. Contrast media kinetic of a lesion is evaluated by placing a region of interest (ROI) over the most enhanced area of the lesion. The more acquisitions are made the more points on the curve and data are available for evaluation. Signal intensity (SI) is calculated relative to the baseline signal intensity value. There are three types of curves that reflect initial contrast enhancement and post initial contrast behavior(35).

The type I curve shows continuous enhancement increasing with time. The type II curve shows a plateau phase after maximum signal intensity is reached 2 to 3 minutes after injection. The type III is a washout curve, which shows a decrease in signal intensity after maximum enhancement has been reached within 2 to 3 minutes (Figure2).

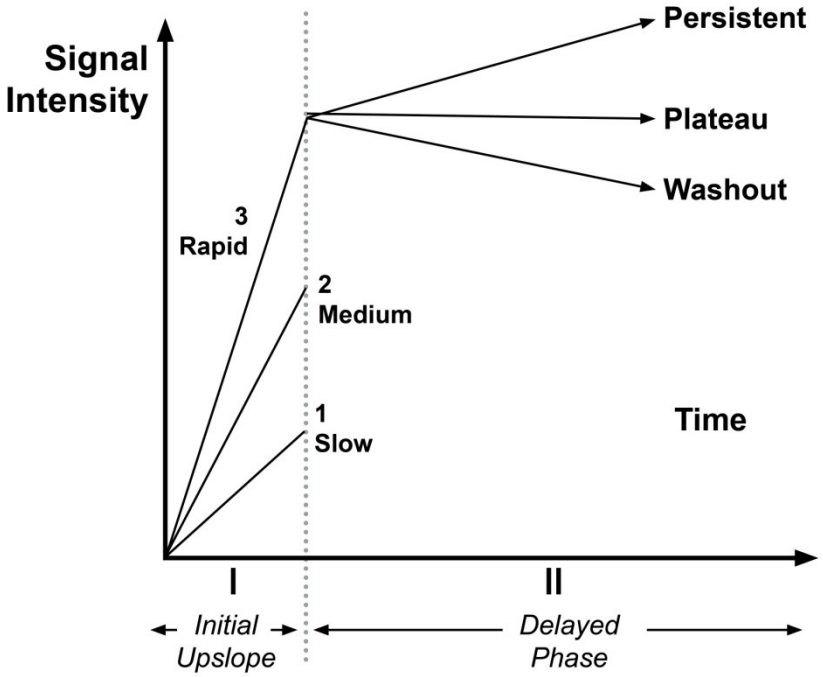

Figure 2. Kinetic curve assessment. Curve interpretation is composed of two sections: I, Initial upslope of curve can be slow (1), medium (2), or rapid (3). This period is the first 2 – 3 minutes of the dynamic scan or until the first change in curve, depending on the dynamic parameters used. II, Delayed phase comprises the period after the first 2 - 3 minutes or until the curve starts to change. Continued increase in enhancement is persistent pattern; steady leveling in enhancement is plateau pattern; and decrease in signal intensity is washout pattern. Washout pattern and plateau pattern occurring early in dynamic study are more likely to be associated with malignancy, whereas persistent pattern is usually detected with benign lesions, such as fibroadenoma, radial scars, and lesions associated with hormonal changes (36).

In addition to the described information of the morphologic and kinetic findings, the MRI report should have a final recommendation. Assessment categories [Table 6] aid understanding the results of the breast MRI studies and they also advances a comparison for scientific research. The terminology is based on BI-RADS categories developed for mammography.

Table 6. BI-RADS Categories

- Assessment Is Incomplete

Category 0

Need Additional Imaging Evaluation:

Finding for which additional imaging evaluation is needed. This is almost always used in a technically unsatisfactory scan, a screening situation in which kinetic imaging has not been done, or when more information is needed to interpret the scan. A recommendation for additional imaging evaluation includes repeating MRI with satisfactory technique, obtaining information from other imaging modalities (mammography, ultrasound, etc.), or correlation with prior breast history. The radiologist should use judgment in how vigorously to pursue previous studies.

- Assessment Is Complete–**Final** Categories

Category 1

Negative:

No abnormal enhancement found; routine follow-up advised. There is nothing to comment on. The breasts are symmetric and no enhancing masses, architectural distortion, or suspicious areas of enhancement are present.

Category 2

Benign Finding(s):

The interpreter may describe a benign finding such as hyalinized non-enhancing fibroadenomas; cysts; old non-enhancing scars; fat-containing lesions such as oil cysts, lipomas, galactoceles and mixed density hamartomas. The interpreter may describe implants while still concluding that there is no mammographic evidence of malignancy.

Category 3

Probably Benign Finding–Short-Interval Follow-Up Suggested:

A finding placed in this category is highly unlikely for malignancy and should have a very high probability of being benign. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability. Data are becoming available that shed light on the efficacy of short-interval follow-up. At the present time, most approaches are intuitive. This will likely undergo future modifications when more data accrue to the validity of an approach includingthe interval required, and the type of findings that should be followed.

Category 4

Suspicious Abnormality–Biopsy Should Be Considered:

These are lesions that do not have the characteristic morphologies of breast cancer but, do have a definite low to moderate probability of being malignant. The radiologist has sufficient concern to urge a biopsy. By subdividing Category 4 into 4A (<25% malignant), 4B (25-50% malignant) and 4C (50-75% malignant) relevant probabilities for malignancy are indicated within this category.

Category 5

Highly Suggestive of Malignancy–Appropriate Action Should Be Taken: (Almost certainly malignant)

These lesions have a high probability (> 75%) of being cancer.

Category 6

Known Biopsy-Proven Malignancy–Appropriate Action Should Be Taken:

A breast cancer that has been proven by histology and is imaged with MRI.

1.7. Purpose

Although mammography provides high surveillance in the management of benign breast lesions, especially among probably benign lesions, MR imaging has shown to be an additional modality for evaluation (37). While multiple studies have shown a cancer rate less than 2% for mammographic lesions classified as BI-RADS 3 (probably benign lesions), the rate of malignancy for MRI BI-RADS 3 lesions still needs further investigation. There are several studies that have evaluated the outcome of probably benign lesions detected with MR-imaging, presenting a wide range of cancer rates (0.6-10%) (38-40) (49-52).

This indicates that the particular MRI features of the lesions, which are placed in this category and the acceptable cancer rate, are not clearly defined.

It is important to determine the appropriate features and follow-up interval of MRI BI-RADS 3 lesions in order to minimize unnecessary biopsy and follow-up imaging.

Furthermore, there are no data available showing results on subsequent malignancy with detected benign lesion.

Therefore, the purpose of this study was to evaluate the negative predictive value of breast MR imaging in patients with lesions classified as BI-RADS 1, 2, and 3, respectively.

2. Materials and Methods

2.1. Study population

In this single center study 1237 women (age, 50±13; range, 18-89) who underwent breast magnetic resonance imaging (MRI) for their first time between May 2000 and May 2007 were retrospectively analyzed. This retrospective, HIPAA-compliant study was conducted after IRB waiver of authorization. Written informed consent for MR imaging was obtained from all of the patients. The larger part of indications was a mammographic finding classified as BI-RADS 0 that was not resolved by diagnostic mammography or ultrasound. Other indications, such as preoperative and postoperative evaluation in woman with known breast cancer, and other reasons (breast pain, nipple discharge etc.), were much less frequent. Out of all patients, a subpopulation with BI-RADS 1, 2, or 3 classifications were eligible for the study. Exclusion criteria were BI-RADS 4, 5, 6 classifications, woman with prior breast cancer, mastectomy, and breast implants.

2.2. Imaging protocol

MR imaging was performed using a dedicated surface breast coil in a 1.5 T system (Magnetom Symphony, Siemens, Erlangen, Germany). The examination was performed in the first half of the menstrual period in premenopausal woman. Menopausal woman under hormone replacement therapy were examined 1 month after discontinuation of treatment.

Images were taken on the axial plane. T2 – weighted turbo inversion recovery magnitude (TIRM) without fat suppression sequence (TR/TE; 4810/80 ms,

matrix; 256/75, FOV; 330 mm, slice thickness 3 mm), followed by T2 – weighted turbo spin echo (TSE) without fat suppression sequence (TR/TE: 3470/99 ms, matrix; 512/70. FOV; 330, slice thickness; 3mm), followed by T1 – weighted 3D-FLASH sequence (TR/TE; 5.13/2.04 ms, flip angle; 12°, matrix; 512/66, FOV; 300 mm, slice thickness; 2mm, totally 1 min 9 s) was used. The entire breast was imaged before and five times (within 6 minutes) after intravenous injection of 0.2 mmol/kg gadopentetate dimeglumine (Omniscan®, GE Healthcare AS Oslo, Norway). Subtracted images were obtained by subtracting pre – contrast images from post contrast images using machines commercially available software. Contrast enhancement was measured using ROI within the lesion in each image. The percentage of signal intensity increase was defined as SI = [(SIpost – SIpre)/SIpre] X 100.

2.3. Analysis

To retrospectively determine the prognostic value of MRM in this group of patients, follow-up was matched with follow up mammography and/or MRM reports and if available histopathology (Figure 3) Adequate follow-up was defined as mammography and/or MRM follow-up and clinical follow-up for at least two years. Statistical analyses and data processing were done using SPSS ® software for Mac ® (version 16.0.1; SPSS) and Microsoft ® Excel ® 2008 for Mac ® (version 12.1.0). Descriptive methods were used to characterize patient data. The negative predictive value (NPV) of MRM in patients classified as MRI BI RADS 1-3 was evaluated. The overall NPV

including all eligible MRI BI-RADS classifications in malignant developments was calculated. In a sub analysis evaluation of the NPV for MRI BI-RADS 1, 2, and 3 categories was performed selectively.

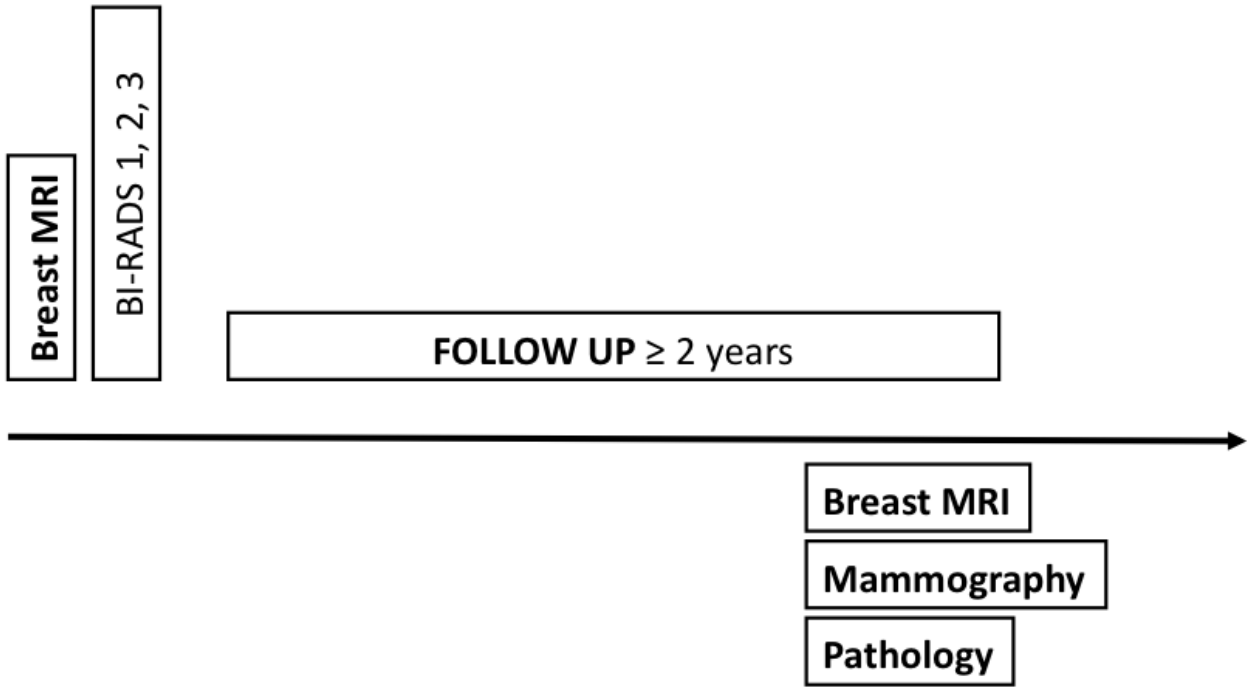

Figure 3. Study design

3. Results

By breast MRI 740 of 1237 patients (59.8%) were classified as BI-RADS 1, 2 or 3 and 525 patients as ≥ BI-RADS 4. Of the patients classified as BI-RADS 1-3, histopathological evaluation of the suspicious lesion was available in 164 patients (22.2%). 84 patients (11.4%) were followed by annual mammography and/or breast MRI over a time interval of at least 2 years (range, 2-9 years) (Figure 7).

By histopathology, 149 lesions were classified as benign and 15 lesions were classified as malignant. The remaining 84 patients without histopathological evaluation of the breast lesion did not exhibit significant changes in symptoms and/or imaging findings during the follow-up period and were therefore classified as benign. The NPV of breast MRI in lesions classified as BI-RADS 1-3 was 93.9%. A subgroup analysis revealed that no patient (0%) with BI-RADS 1, four patients (1.6%) with BI-RADS 2, and 11 patients (4.4%) with BI-RADS 3 developed a malignant breast lesion [Table 7].

Table 7. Occurance of malignancy related to the **MRI BI-RADS´classification and negative predictive value (NPV) for the classification I - III**

BI-RADS	Diagnostic value	N (%)	NPV
I	Negative	0 (0%)	
II	Benign	4 (1.6%)	
III	Probably benign	11 (4.4%)	
Total			93.9 %

4. Discussion

MRM has altered clinical management for woman with breast cancer. The majority of patients referred for breast MR imaging are patients at high risk, patients with a new breast cancer diagnosis, patients who underwent neoadjuvant chemotherapy, and patients with inconclusive mammography and ultrasound. When applied in these clinical indications, the high sensitivity of breast MRI results in early cancer detection compared to other tests for breast carcinoma. The limitations of breast MRI are its high cost and low specificity leading to false positive results that require imaging follow-up or biopsy. The current study aims to provide further establishment for the predictive value in patients classified as MRI BI-RADS 1,2, and 3 with breast MRI.

Several studies have reported the diagnostic significance for probably benign lesions and the risk of developing a malignancy during follow up (38-40) (49-52). In these investigations of heterogeneous study populations the frequency of malignancy for assessed MRI BI-RADS 3 lesions has been reported 0.6-10%. This wide range of cancer within MRI BIRADS 3 classification shows that the particular MRI features of the lesions, which are placed in this category and the corresponding cancer rate, are not clearly defined.
There is no data available on lesions classified as MRI BI-RADS 1 and MRI BI-RADS 2 and the outcome during follow-up.

Lesions with an initial probably benign classification in mammography have shown a rate of malignancy <0.5 %. (41). Thus, Sickles et. al (41) defined a

short term follow up protocol for mammographically detected probably benign lesions at 6 months followed by mammography of both breasts at 1, 2, and 3 years after the initial mammogram. This data in association with other studies are supporting the scientific evidence of the short-term follow up protocol (42-46). The mammographic BI-RADS 3 category is well established and implements low costs and reduces the biopsy rate. Therefore, patients with probably benign lesions assessed as BI-RADS 3 receive a large benefit of follow-up mammograms considering risk of anesthesia, cosmetic outcomes and morbidity of the procedure.

However, many benign findings placed into the probably benign MRI category may result in overutilization of breast MR imaging and in unnecessary anxiety of the patients.

Malignancy occurred in lesions initially interpreted as MRI BI-RADS 3 in 4.4%. As previously reported these values are higher than the 0.2 – 2% frequencies of breast carcinomas shown in studies of non-palpable, mammographically detected probably benign lesions. (42-46).

However, comparable investigations have shown a 0.6-10% frequency of malignancy solely in MRI BI-RADS 3 lesions. (38-40, 49-52).

There are limited data available on the outcome of patients with benign (MRI BI-RADS 1 – 3) classifications on the initial breast MRI. In our study, subsequent malignancy was found in 1.6% of lesions initially classified as MRI BI-RADS 2. However, these lesions have not been able to be differentiated entirely from de novo lesions. This has to be considered as a major limitation of our study. .

The diagnostic value of breast MRI is continuously discussed. High sensitivity and detection of cancers that are occult on mammography, ultrasound, and clinical breast examination are the major benefits of breast MRI. Nevertheless, low specificity from overlap in the imaging features of benign and malignant lesions tempers its advantages.

The use of breast MRI is steadily increasing and therefore also the rate of lesions solely detected with MRI. If these lesions are suspicious to be malignant, histopathology evaluation is recommended. To reduce the rate of false positive biopsies in benign lesions, breast MRI should accurately maximize the prediction of malignancy through all its imaging features (47). It has been shown that the conjunction of different breast lesion interpretation criteria to obtain a total breast MRI score, such as the Göttinger Score, and its translation into BI-RADS® is adventegous in case of lesions detected solely with breast MRI. It allows standardized MRI BI-RADS® classification with ensurable positive predicve values of malignancy for each MRI BI-RADS® category(48).

Although the current study is based on a retrospective analysis, the results have been established from 248 patients, which is a high number compared to previous investigations (38-40). Investigations focused solely on the final BI-RADS recommendation in the MRI report. Therefore, individual experience of the radiologist could probably have led to false interpretations of the imaging findings resulting in false MRI BI-RDAS classification (Figure 4). The breast MR imaging studies have been reviewed by three different radiologists, and the results reflect the interobserver variability in breast MRI interpretation

and, therefore, the variability in routinely performed breast MR imaging studies.

In conclusion breast MRI shows a high negative predictive value of 93.9 % in lesions classified as BI-RADS 1-3. Lesions classified by MRI as probably benign (BI-RADS 3) showed a higher frequency of developing malignant disease compared to lesions classified as BI-RADS 1 or 2. In this subgroup of patients 4.4% of lesions developed malignancy, which is a higher rate compared to mammographically BI-RADS 3 lesions. Therefore, appropriate assessment which lesions should receive a follow-up MRI and which lesions should be classified as BI-RADS 3 has to be performed. Training of radiologists and further classification improvements is necessary.

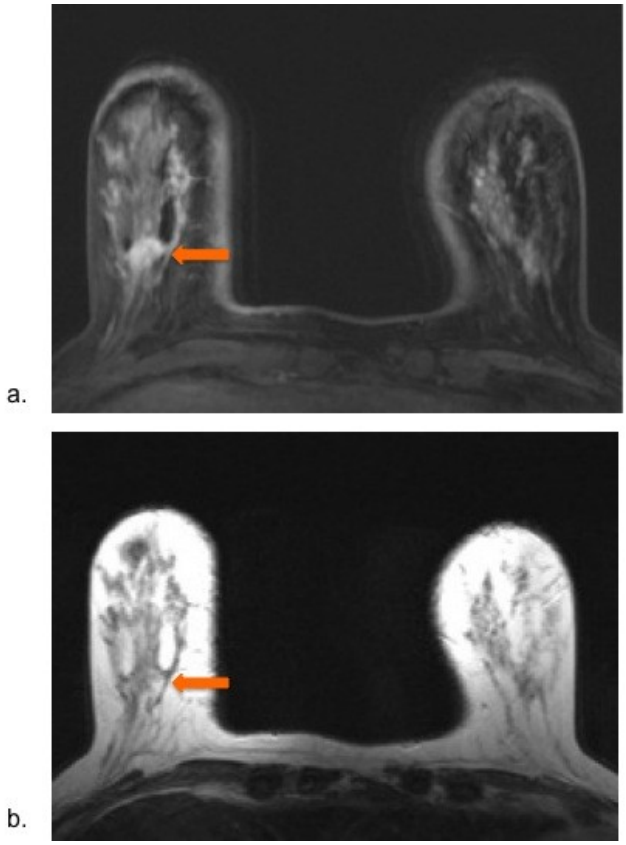

Figure 4. Breast MRI case

Fourty-seven-year-old woman who has been referred for breast MRI one year after biopsy proven fibrotic mastopathy in the right breast and ductal epithelic hyperplasia without atypia. Breast MRI showed an axial 1.1 cm x 1 cm lobular expansive lesion with an early contrast enhancement and a plateau curve (arrow) (a, b). Morphology features are suspect for a Fibroadenoma and MRI was classified as BI-RADS 3.

Follow-up breast MR six months later didn't show significant changes.

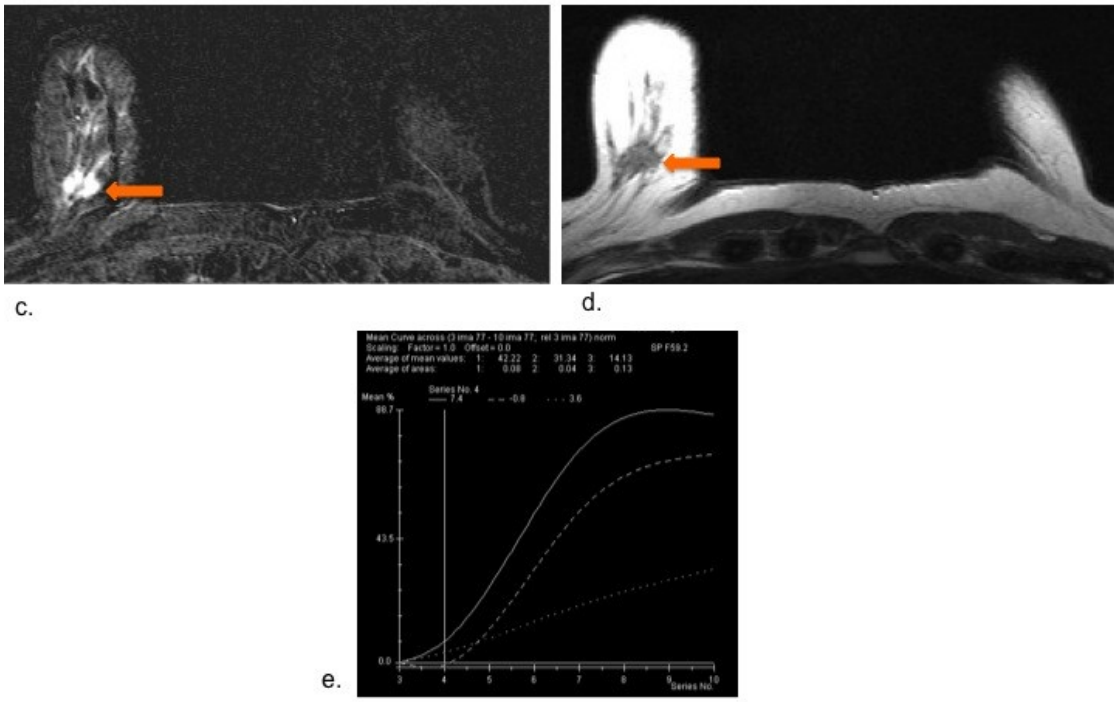

Figure 4. Breast MRI case

After twenty-three months breast MRI in the same patient revealed an enlargement of the lesion (1.4 cm x 1.1 cm) (arrow) (c, d). The lesion appeared demarcated and hypointense in the center. The kinetic behavior didn't show significant changes and remained to be a plateau curve (e). Due to the change in size the lesion was classified as BI-RADS IV and biopsy has proven an invasive ductal carcinoma.

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6. Figure Legends

6.1. List of Figures

6.2. List of Tables

8. Resume

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