New diagnostic developments to prevent unnecessary invasive procedures in breast cancer diagnostic work-up

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Chapter 1

General Introduction

Introduction

Worldwide incidence of breast cancer is higher than incidence of other malignancies among women. In the Netherlands approximately one out of eight women will develop breast cancer during life [1]. Five to ten per cent of all breast cancers are hereditary. In the Netherlands, approximately 20% of familial breast cancer is caused by BRCA1, 5% is caused by BRCA2 and the remainder of 75% is non-BRCA1/BRCA2 [2]. Although the incidence has increased, mortality has decreased during the last two decades and at the moment the risk of dying of breast cancer is 1 of 26 [3]. This reduction in mortality is partly due to early detection of malignancies in screening and partly due to more and better adjuvant therapies [4].

Mammography

Mammography is the primary imaging modality for the early detection of breast cancer. Despite advances in mammographic techniques (digital), mammography still has its limitations with regard to both sensitivity (39%-86%) and specificity (88%-94%), which depends on age and breast density [5,6,7]. Younger women have more fibroglandular tissue, resulting in a dense mammogram, with a low sensitivity.

A diagnostic mammographic examination usually consists of craniocaudal and mediolateral oblique views in accordance with the National Breast Cancer Consultation in the Netherlands (NABON) and the American College of Radiology (ACR) standards [8,9]. Today, the ACR Breast Imaging Reporting and Data System (BI-RADS) is the communication tool in mammography reports. Each mammographic feature is described in the BI-RADS lexicon. The lexicon includes the following mammographic images: masses, micro/macrocalcifications, architectural distortions and special cases including ductal ectasia, intramammary lymph node or focal asymmetric density. After mammographic assessment by the radiologist, the mammograms are coded using the ordered categories of the ACR BI-RADS lexicon: category 1, negative (normal finding); category 2, benign finding; category 3, probably benign; category 4, suspicious finding; category 5, highly suggestive of malignancy and category 6, pathologically proven breast cancer [9].

The diagnostic work-up of breast lesions depends on the BI-RADS classification of the breast lesions. The guideline for non-invasive diagnostic tests for breast abnormalities of the Agency for Health Care Research and Quality in the United States (AHRQ) and the guideline of the NABON state that breast lesions classified as BI-RADS 1 and 2 require no further work-up or follow-up other than routinely required [8,10]. The probability of a BI-RADS 3 lesion being cancer is considered to be less than 2 %. The work-up of a BI-RADS 3 lesion should be a biopsy or follow up mammography after six months [8,10]. In practice, the work-up of BI-RADS 3 lesions is decided by the possibilities for biopsy procedures, but also the wish of the patient and the preference of the radiologist. The additional value of breast Magnetic Resonance Imaging (MRI) as a non-invasive tool for the work-up of BI-RADS 3 lesions is still under debate [8,10]. The chance of malignancy for a BI-RADS 4 lesion varies from 2 to 95% and for a BI-RADS 5 lesion the chance of malignancy is higher than 95%. Therefore, the work-up for these categories requires an invasive (biopsy) procedure [8,10]. This biopsy procedure cannot be replaced by breast MRI, because histology is obligatory in these cases.

BI-RADS classification remains a radiological classification with disregard of clinical and prognostic factor. Inter and intra observer variability thus is a recognised problem in images which are difficult to classify, especially in the BI-RADS 3 and 4 categories [11-15]. In conjunction with this limited accuracy of both physical examination and mammography results in a large majority of patients referred for biopsy with a BI-RADS 3 lesion to a final (pathologically proven) benign diagnosis.

Breast Magnetic Resonance Imaging

Breast MRI has emerged as a clinically useful additional diagnostic modality [16]. At present the major validated clinical indications for breast MRI are: the identification of breast cancer in high risk patients, the evaluation of multicentricity or multifocality in primary breast cancer detected by other methods, the detection and location of mammographic and ultrasound occult cancer in women with axillary metastases, the evaluation of treatment response during neoadjuvant chemotherapy, the evaluation of nipple discharge, imaging of the breast after conservative therapy, imaging of prothesis and the evaluation of inconclusive findings in conventional imaging [16-20]. Scientific

evidence supports the use of breast MRI for specific clinical indications, although data are lacking to support the use of MRI for clinical scenarios [17,18]. It is not yet common practice to use breast MRI as problem solving modality, because thorough data validating its use in the case of challenging or inconclusive mammographic findings are not yet available [21-27].

Kuhl [16] described in detail why the evidence for the effectiveness of breast MRI in helping to solve focal mammographic problems is relatively weak. The reason is that ultrasonography- or mammography-guided core or vacuumbiopsy can obtain histological proof of equivocal lesions. A variety of minimally invasive procedures is widely available, relatively safe, inexpensive and giving diagnosis without surgical intervention. Furthermore, breast MRI has its limitations which include higher costs, longer examination time, and lower availability when compared with mammography and ultrasound [16,17].

However, in general MRI can be used as problem solving modality when the findings of conventional imaging are inconclusive, because the sensitivity of breast MRI, which usually exceeds 90%, is the highest of all imaging techniques for breast lesions [21,28,29]. Furthermore, a negative breast MRI meets a sufficiently high negative predictive value (NPV) (91.7%-100%) for non-calcified breast lesions to safely rule out malignancy [24,27,30,31] and thus prevent unnecessary invasive diagnostic procedures.

As for mammography and ultrasound, also for contrast-enhanced MRI an ACR BI-RADS breast lexicon was published in 2003 based on the same objectives and methodology [9]. The lexicon includes the following MR findings: focus/foci, mass enhancement and non-mass-like enhancement. For imaging analysis the dynamic breast MR images are used. In the contrast-enhanced dynamic sequence the uptake of contrast medium in breast lesions is followed in time. With the use of the dynamic breast MR images the morphological characteristics (shape, margin, spatial distribution and internal architecture) and the enhancement pattern of breast lesions are assessed [32-34]. Specific patterns of dynamic enhancement curves have been defined as persistent (type 1), plateau (type 2) and washout (type 3). Persistent enhancement is characterized by a monotonic increase, plateau enhancement by a constant level or “plateau” and the washout pattern has a characteristic peak followed by an immediate decrease in the signal intensity. Type 1 contrast enhancement has been shown to be suggestive of a benign lesion, whereas type 3 contrast

enhancement is highly associated with breast cancers. However, a type 2 plateau enhancement pattern can be seen in both benign and malignant lesions [35-36]. After breast MRI evaluation by the radiologist, the MRI scans are also coded using the ordered categories of the ACR BI-RADS lexicon [9] and in analogy with the guideline of AHRQ and NABON the diagnostic work-up of breast lesions also depends on the BI-RADS classification [8,10].

Because the postprocessing and interpretation of breast MRI data is time consuming and operator dependent, Computer Aided Detection (CAD) programs for MR imaging of breast lesions have been developed attempting to standardize and facilitate the interpretation of breast MRI [37,38].

Computer Aided Detection system

The first CAD system for breast MRI (CADstream by Confimra, Inc) was launched in January 2003. It was not primarily developed to identify breast lesions, because most lesions are already detected by the radiologist. CAD for breast MRI can be defined as: "The automated analysis of enhancement kinetics, highlighting features related to malignancy" [38] and can, therefore, assist the radiologist in determining which lesions are benign and which are malignant.

CAD systems help the radiologist to interpret breast MRI by automating extraction and interpretation of kinetic curves (the enhancement pattern of lesions). Using a CAD system, curve extraction and thresholding result in angiogenesis maps, which standardize the interpretation of breast MRI according to the BI-RADS lexicon. The angiogenesis maps provide a fast and reproducible way to take images from nearly any breast MR acquisition protocol and highlight features correlated with malignancy.

The automated kinetic assessment of CAD generates a colour-coding based on the signal intensity changes in voxels during the enhancement of the breast tissue. Colour-coding provides a quick way for radiologists to find areas of significant enhancement and to interpret the kinetic curve (persistent, plateau and washout curve) [37,38]. The angiogenesis maps and colour-coding may help radiologists to identify lesions based on morphological and kinetic features and to make a more "evidence based" decisions regarding management of suspicious breast lesions. Therefore the implementation of CAD software for breast MRI

should automatically identify (almost) all non-calcified lesions suspected of malignancy at mammography. This is reflected by a very high sensitivity and NPV for these non-calcified breast lesions.

MR spectroscopy

Despite good evidence that breast MRI has a high NPV for non-calcified breast lesions, there is overlap in enhancement between benign and malignant breast lesions in a subcategory of patients [31-36]. Carcinomas tend to enhance faster and washout earlier than benign lesions do, but there are numerous exceptions to this pattern, for example fibroadenomas incidentally demonstrate an enhancement pattern similar to that of invasive cancer [39]. Therefore, in some cases, enhancement patterns may be equivocal and additional diagnostic methods may be needed for clarifications. This is mostly the case for breast lesions which are classified as BI-RADS 3 on MRI (unequivocal enhancement curve, type 2). The probability of MRI BI-RADS 3 lesions being cancer is not yet clear. Although this percentage should be less than 2 %, in the literature the chance of malignancy for MRI BI-RADS 3 lesion varies from 0.6% to 10% [30,40-43].

In addition to morphological and kinetical analysis, metabolic information is expected to be promising for the final diagnosis of breast lesions. In vivo proton (^{1}H) MR spectroscopy of the breast provides metabolic information about the investigated tissue in a non-invasive manner. It has shown that substantial levels of choline-containing compounds can be detected in breast cancer, whereas choline generally is at least one order of magnitude lower in concentration in normal fibroglandular tissue [44]. However, it has been suggested that choline levels may not be highly elevated in all breast cancers. This might be determined by the biologic aggressiveness; thus, the ability of MR spectroscopy to demonstrate abnormal choline levels in breast cancer has been variable [45].

MR spectroscopic studies of the human breast have been either single-voxel [44-64] or multivoxel [65-70] investigations. *Single-voxel* spectroscopy is based on one voxel (one single rectangular volume of interest) placement in the breast lesion. In this voxel elevated levels of choline compounds which yield a signal at a chemical shift of 3.2 ppm are detected in the case of malignant tumor [46,47]. With rare exceptions [44,47,55,57], in the above clinical studies the metabolites detected by single-voxel MR spectroscopy were

documented in, at best, a semiquantitative fashion such as assessment of the signal-to-noise ratio in the choline peak, peak visibility, or nonreferenced arbitrary peak area units. In several single-voxel MR spectroscopic studies performed on 1.5T MR imagers, investigators have reported sensitivities of 70%-100% and specificities of 82%-100% [46-52,56]. However, the single-voxel technique has limitations in terms of lesion coverage, which may affect the sensitivity of assessing choline from just one voxel in view of tumor heterogeneity [65]. Furthermore, the study of local pathology by single-voxel MR spectroscopy will always be hampered by the impossibility to study tissue heterogeneity or to compare the metabolite signals in a breast lesion directly to those in unaffected tissue [65]. Problems inherent to single-voxel MR spectroscopy may thus have influenced the diagnostic accuracy (sensitivity, specificity) of this novel MRI method in a negative way.

Multivoxel technique or chemical-shift imaging (CSI) can be used to acquire spectroscopic information from a large volume of interest subdivided into an array of voxels measured in a single measurement, and hence is suitable for analyzing the regional distribution of tumor metabolites. Therefore, the multivoxel MR spectroscopic technique is suitable for analyzing the regional distribution of tumor metabolites and to study tissue heterogeneity. Another opportunity of multivoxel MR spectroscopy is presented by the possibility of metabolic mapping of breast lesions. Although it is commonly used in the brain and prostate, only six studies with breast lesions have been reported [65-70]. In 3 of these studies [65-67] the diagnostic value of combined contrast-enhanced MRI and multivoxel MR spectroscopy in evaluating breast lesions is assessed. It appears that multivoxel MR spectroscopy is a promising technique for classification of breast lesions when contrast-enhanced MRI results are equivocal. However, multivoxel MR spectroscopic studies, while potentially allowing for truly quantitative tissue characterization, have up to now also been far from quantitative with the use of the choline signal-to-noise ratio as measure of tumour activity [65-70]. Quantitative tissue characterization is necessary because choline signals are not only detected in malignant lesions but also in benign breast lesions and normal fibroglandular tissue. Therefore, the presence of a Cho-related peak in breast MR spectroscopy is not sufficient for a final non-invasive diagnosis of malignancy.

With the development of a protocol for quantitative multivoxel MR spectroscopy for the examination and metabolic mapping of breast lesions, the choline compounds peak could

be determined more accurately leading to enhancement of the diagnostic use of MR spectroscopy. A quantitative measurement of choline concentrations would thus increase the accuracy of contrast-enhanced MRI in the assessment of breast lesions. In this way it should be possible to exclude patients with benign breast lesions from further invasive diagnostic work-up.

Purpose and outline

The focus of this PhD thesis is to investigate new non-invasive diagnostic developments to prevent unnecessary invasive procedures in breast cancer diagnostic work-up for women with a probably benign (BI-RADS 3) breast lesion. Therefore, in a meta-analysis (chapter 2) the usefulness of breast MRI as a problem solving modality in patients with mammographic BI-RADS 3 lesions is analyzed. In chapter 3 the NPV of breast MRI in mammographic BI-RADS 3 lesions is investigated. The purpose is to determine whether breast MRI can provide a sufficient NVP to safely rule out malignancy and decrease the percentages of invasive diagnostic procedures. In a systematic review and meta-analysis in chapter 4 the sensitivity and specificity of radiologist and resident in the assessment of breast lesions on MRI with and without a commercial available CAD system is evaluated. In chapter 5 a quantitative multivoxel MR spectroscopic method for the examination and metabolic mapping of breast lesions is presented. The optimal cutoff of choline concentration in quantitative multivoxel MR spectroscopic data to safely prove benignancy in breast lesions is examined in chapter 6. Lastly, in chapter 7 the added value of quantitative multivoxel MR spectroscopy in breast MRI is investigated. If multivoxel MR spectroscopy can increase the accuracy of breast MRI, this could prevent unnecessary invasive diagnostic work-up for patients with benign lesions.

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Chapter 2

Breast magnetic resonance imaging as a problem-solving modality in mammographic BI-RADS 3 lesions

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Abstract

The probability of a mammographic Breast Imaging Reporting and Data System (BI-RADS) 3 lesion being cancer is considered to be less than 2 %. Therefore, the work-up of a mammographic BI-RADS 3 lesion should be biopsy or follow-up mammography after 6 months. However, most patients referred for biopsy have benign disease. Although the negative predictive value (NPV) of magnetic resonance imaging (MRI) is highest of all imaging techniques, it is not yet common practise to use breast MRI as problem-solving modality to exclude patients for further diagnostic work-up. Therefore, in this meta-analysis, the usefulness of breast MRI as a problem-solving modality in mammographic BI-RADS 3 lesions is investigated. After a systematic search only 5 out of 61 studies met the inclusion criteria. The NPV in 2 of those studies was reported to be 100%. It was concluded that MRI can be used as an adjunctive tool to mammographic BI-RADS 3 findings to exclude patients for further diagnostic work-up. The other 3 studies assessed the accuracy of MRI in mammographic BI-RADS 3 microcalcifications. These studies reported a NPV of MRI between 76% and 97%. Therefore, MRI cannot be implemented as a diagnostic tool to evaluate mammographic microcalcifications at this time. The first solid data indicate that breast MRI might be useful as a problem-solving modality to exclude patients with non-calcified mammographic BI-RADS 3 lesions for further diagnostic work-up. However, further research is needed to verify these results.

Introduction

Mammography is the primary imaging modality for the early detection of breast cancer. Despite advances in mammographic techniques (digital), mammography still has its limitations with regard to both sensitivity (65.6-85.5%) and specificity (87.7-94.3%) [1,2]. Mammograms are coded using the ordered categories of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon: category 1, negative; 2, benign finding; 3, probably benign; 4, suspicious finding; 5, highly suggestive of malignancy [3]. The diagnostic work-up of breast lesions depends on the BI-RADS classification of the breast lesions. The guideline for non-invasive diagnostic tests for breast abnormalities of the Agency for Health Care Research and Quality in the United States (AHRQ) states that breast lesions classified as BI-RADS 1 and 2 require no further work-up or follow-up other than routinely called for [4]. The chance of a BI-RADS 4 lesion to be malignant varies from 2% to 95%, whereas this chance is over 95% for a BI-RADS 5 lesion [4]. Therefore, the work-up for these categories demand a biopsy procedure. This biopsy procedure cannot be replaced by breast magnetic resonance imaging (MRI), because histology is obligatory in these cases [4]. The most difficult mammographic lesions are the lesions which are classified as BI-RADS 3. The probability of a BI-RADS 3 lesion being cancer is considered to be less than 2 %. For the work-up of BI-RADS 3 lesion biopsy or follow-up mammography after six months is advised [4]. In practice, the decision on the work-up of BI-RADS 3 lesions depends on the possibilities for biopsy procedures, the wishes of the patient and the preference of the radiologist. Most patients who are referred for a biopsy have benign disease because of the low predictive value of both physical examination and mammography [5,6]. The value of breast MRI in BI-RADS 3 lesions is not yet clear [4]. Breast MRI is emerging as a clinically useful additional diagnostic tool [4,7] and has an excellent sensitivity and negative predictive value (NPV), which usually exceeds 90% [8-10]. However, the overall specificity of breast MRI varies between 67% and 72% [8-10]. The diagnostic accuracy of breast MRI varies with the expertise of the radiologist and the particular patient population studied. It is important that breast MRI is used for those groups of patients for whom there is evidence of acceptable diagnostic accuracy. Breast MRI as first-line imaging modality is performed by screening women at

increased risk for breast cancer [7,11-14]. As second-line modality, breast MRI can be used for the following indications: inconclusive findings in conventional imaging, preoperative staging, axillary node malignancy and unknown site of primary tumor, the evaluation of therapy response in the neoadjuvant chemotherapy setting [7,11-14], imaging of the breast after conservative therapy, prothesis imaging [7,13], nipple discharge [7,14] and MR-guided biopsy and lesion localization [13]. Although the NPV of MRI in breast cancer is the highest of all imaging techniques [8;15,16] and in most of the cases a negative breast MRI excludes malignancy [17-19], it is not yet common practise to use breast MRI as problem-solving modality in excluding patients for further diagnostic work-up.
Therefore, in this meta-analysis, the usefulness of breast MRI as a problem-solving modality in patients with mammographic BI-RADS 3 lesions is investigated.

Materials and methods

Search strategy

A computerized search was performed to identify relevant studies in Medline and Embase up to 2010. The following strategy was followed in Medline: "Magnetic Resonance Imaging" [Mesh term] OR “Magnetic Resonance Imaging” [Text Word] OR “MRI” [Text Word] OR “MR imaging” [Text Word] AND "probably benign lesions" [Text Word] OR “microcalcifications” [Text Word] OR “inconclusive findings” [Text Word] AND “mammography” [Mesh term] OR “mammography” [Text Word] AND "Sensitivity and Specificity" [Mesh term] OR “specificity OR sensitivity” [Text Word]. In Embase the same strategy was used. All languages were considered.

Eligibility criteria and study selection

Medline and Embase were searched for studies that used breast MRI as problem-solving modality in mammographic BI-RADS 3 lesions. Studies were included if the following inclusion criteria were met: (1) all patients underwent a mammography and breast MRI; (2) study population had mammographic BI-RADS 3 lesions or mammographic BI-RADS 3 microcalcifications; (3) accuracy, sensitivity, specificity, positive predictive value (PPV) and/or negative predictive value (NPV) was/were measured; (4) studies with original data

which were published in peer-reviewed journals. The selected relevant studies were based on title, abstract and full paper. All selected studies were published in English language.
The complete search yielded 61 studies, of which 9 studies were duplicates. Forty-one out of the 52 studies were excluded based on the title. From the 11 remaining studies the abstract or full paper was reviewed. Four studies were excluded because no BI-RADS classification was used and 2 studies were reviews. Only 5 studies [20-24] met the inclusion criteria.

Results

In the 5 selected studies 376 breast lesions were reported, of which 213 were microcalcifications, 110 were asymmetric mammographic finding, 36 were non-calcified regular shaped lesions, 12 were architectural distortion and 5 were scar lesions. In 2 [22,23] studies mammographic BI-RADS 3 lesions were included; one [22] only included category 3 lesions, the other [23] also included BI-RADS 0 and 4 lesions. In the other 3 [20,21,24] studies mammographic BI-RADS 3 microcalcifications were included but microcalcifications that were classified as BI-RADS 4 and 5 were also included (Table 1).

Mammographic BI-RADS 3 lesions

In one study [22], the role of MRI in the evaluation of mammographic BI-RADS 3 lesions was investigated. MRI was performed on 56 lesions described as BI-RADS 3 by mammography in 43 patients. The 56 mammographic BI-RADS 3 lesions were distributed into non-calcified regular shaped lesions (64.3%), focal asymmetric densities (21.4%), generalized microcalcifications (12.6%) and a cluster of tiny calcifications (1.7%). The sensitivity, specificity, accuracy, PPV and NPV of MRI in the determination of malignancy in these mammographic BI-RADS 3 lesions were calculated as 100%, 96.4%, 96.4%, 33.3% and 100%, respectively. Gokalp et al. [22] concluded that MRI may be helpful in the evaluation of focal asymmetric densities as MRI confirmed that nine of the 12 mammographic focal asymmetric densities were breast tissue and that the other 3 were masses.

Table 1 Study characteristics (P, prospective; R, retrospective; c, consecutive; NR, not reported).

	Study (first author, year of publication)				
	Moy 2009[23]	Gokalp 2006[22]	Akita 2009[20]	Cilotti 2007[21]	Uetmatsu 2007[24]
No. of patients	115	43	53	55	96
Study design	R,c	P,c	NR	NR	P,c
No. of lesions	115	56	50	55	100
Mammographic findings					
Asymmetry	98	12			
Architectural distortion	12				
Scar lesion	5				
Non-calcified regular-shaped lesions		36			
Generalized calcifications		7			
A cluster of tiny calcifications		1			
Microcalcifications			50	55	100
Mammogrraphic BI-RADS					
0	78				
1					
2					
3	15	56	9	23	55
4	22		41	25	27
5				7	18
Gold standard	Pathology	Pathology, FU 6 months	Pathology	Pathology	Pathology
Mammography[a]					
Sensitivity	NR	NR	100%	77%	NR
Specificity	80.7%	NR	24%	59%	NR
PPV	8.7%	NR	NR	63%	67%
NPV	NR	NR	NR	74%	93%
Accuracy	78.3%	NR	44%	67.2%	NR
MRI[a]					
Sensitivity	100%	100%	85%[b]	73%	NR
Specificity	91.7%	96.4%	100%[b]	76%	NR
PPV	40%	33.3%	NR	73%	86%
NPV	100%	100%	NR	76%	97%
Accuracy	92.2%	96.4%	96%[b]	74.5%	NR

[a] In the analysis of Moy et al., Cilotti et al. and Uematsu et al. BI-RADS 3 lesions were considered as benign and BI-RADS 4 and 5 as malignant.
[b] Mammography+MRI.

Another study [23] evaluated the usefulness of breast MRI in cases of inconclusive mammographic or sonographic findings. In this study, not only mammographic BI-RADS 3 lesions (n=15) were included, but also BI-RADS 4 lesions (n=22) and mammographic BI-RADS 0 lesions (n=78). In total, 115 breast MRI scans were used as adjunctive tool and the findings were correlated with pathology. The equivocal mammographic findings for which MRI was performed were asymmetry without associated microcalcifications (85.2%), architectural distortion (10.4%) and change in the appearance of the site of a previous benign biopsy finding (4.3%). MRI had a sensitivity of 100%, NPV of 100% and compared with mammography had significantly higher specificity (91.7% versus 80.7%, p=0.029), PPV (40% vs 8.7%, p=0.032), and overall accuracy (92.2% vs 78.3%, p=0.00052). Moy et al. [23] concluded that breast MRI can be a useful adjunctive tool when equivocal findings at conventional mammography are asymmetry or architectural distortion.

Mammographic BI-RADS 3 microcalcifications

Three published studies [20,21,24] evaluated the role of MRI in patients with mammographic BI-RADS 3 microcalcifications. Akita et al. [20] included also mammographic BI-RADS 4 microcalcifications and Cilotti et al. [21] and Uetmatsu et al. [24] included mammographic BI-RADS 4 and 5 microcalcifications.

In the study of Akita et al. [20] the clinical value of additional breast MRI in patients with microcalcifications on mammography and negative ultrasound findings was evaluated. Fifty patients with mammographic microcalcifications (9 BI-RADS category 3 and 41 BI-RADS category 4) were included. These patients underwent MRI before stereotactic vacuum-assisted biopsy. Mammography had a sensitivity of 100%, a specificity of 24% and an accuracy of 44%, whereas mammography plus MRI had a sensitivity of 85%, a specificity of 100% and an accuracy of 96%. They concluded that breast MRI compared with mammography alone significantly improved the rate of diagnosis of malignancy in breast lesions which were detected as mammographic BI-RADS 3 or 4 microcalcifications [20].

In the study of Uematsu et al. [24], breast MRI was performed in 100 microcalcifications detected at screening mammography in 96 patients. These patients also underwent a stereotactic vacuum-assisted biopsy as gold standard. PPVs and NPVs were calculated on

the basis of a BI-RADS category and the absence or presence of contrast uptake in the area of microcalcifications. NPV of BI-RADS mammography 3 was 93% versus 97% NPV of MRI (p=0.167). The PPV of contrast uptake of MRI was 86%, which is significantly higher than the 67% PPV of BI-RADS mammography 4 and 5 (p=0.033). Uematsu et al. [24] concluded that the imperfect PPVs and NPVs of MRI in the evaluation of microcalcifications detected at screening cannot replace stereotactic vacuum-assisted biopsy.

Also Cilotti et al. [21] concluded that the PPV and NPV of MRI in the characterization of microcalcifications are not high. In their study, 55 patients with mammographic calcifications classified as BI-RADS categories 3, 4 or 5 underwent MRI and stereotactic vacuum-assisted biopsy. The sensitivity, specificity, PPV, NPV and diagnostic accuracy were 73%, 76%, 73%, 76% and 74.5%, respectively. Their conclusion is that MRI cannot be considered a diagnostic tool for evaluating microcalcifications [21].

Discussion

The AHRQ guideline states that the work-up for mammographic BI-RADS 3 lesions should be biopsy or follow-up imaging after 6 months [4]. There is not yet a role for breast MRI, because ultrasonography- or mammography-guided core or vacuumbiopsy can obtain histological proof of a BI-RADS 3 lesion. A variety of minimally invasive procedures is widely available, relatively safe, inexpensive and provide a diagnosis without surgical intervention. Furthermore, breast MRI has its limitations, which include higher costs, longer examination time, and lower availability compared with mammography and ultrasound [7,11]. If breast MRI wants to be an effective addition to the work-up of a mammographic BI-RADS 3 lesion, the NPV of breast MRI must be sufficiently high to definitively rule out further work-up with biopsy. Although there were only 5 studies which investigated the usefulness of MRI as problem-solving modality in mammographic BI-RADS 3 lesions, the NPV was 100% in non-calcified mammographic BI-RADS 3 lesions and 76-97% in mammographic BI-RADS 3 microcalcifications. On the other hand Kuhl [7] indicated that the evidence for the effectiveness of breast MRI is relatively weak in helping to solve mammographic problems, because in a multicenter trial of Bluemke et al. [8] the

NPV was not high enough to exclude malignancy with sufficient confidence in case of an equivocal or suspicious lesion seen at conventional imaging. The diagnostic accuracy of MRI was studied in 821 patients with a suspicious mammographic BI-RADS 4 or 5 lesion (85%) or a suspicious clinical finding with a negative or benign conventional work-up (15%) before biopsy. MRI had a NPV of 85% with cancer missed in 48 of 329 negative MRI examinations. This NPV is not sufficiently high to avoid biopsy in suspicious mammographic BI-RADS 4 or 5 lesions [8]. This widely referenced multicenter study was performed in 14 hospitals from 1998 to 2001 and therefore used now outdated MR equipment. Furthermore, the study of Bluemke et al. [8] included patients with microcalcifications of the breast which have a negative influence on the NPV. In this meta-analysis 3 studies [20,21,24] assessed the role of MRI in mammographic BI-RADS 3 microcalcifications. These studies also included microcalcifications BI-RADS 4 and 5. A NPV between 76% and 97% was reported [21,24] in concordance with Bluemke results [8]. Therefore, MRI cannot be implemented as a problem-solving modality in mammographic microcalcifications at this time. Mammography and stereotactic biopsy remain the only techniques for characterising microcalcifications [21,24].

According to Kuhl et al. [7] MRI can be useful as an additional tool in patients with calcifications: it can be helpful in demonstrating or excluding underlying invasive cancer, because MRI has a high NPV for invasive cancer. An important application of MRI associated with suspicious microcalcifications could be to evaluate disease extension [7].

However, the studies which comply with the inclusion criteria of the meta-analysis, i.e. non-calcified mammographic BI-RADS 3 lesions [22,23], reported a NPV of 100% and concluded that MRI can be a useful tool in mammographic BI-RADS 3 lesions, especially when mammographic findings are asymmetry or architectural distortion [22,23].

Although there are sparse data, the first solid data indicate that breast MRI might be useful as problem-solving modality to exclude patients with non-calcified mammographic BI-RADS 3 lesions from further diagnostic work-up. However, further research is needed to verify these results.

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Chapter 3

The negative predictive value of breast Magnetic Resonance Imaging in noncalcified BIRADS 3 lesions

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Abstract

Purpose: The purpose of this study is to determine whether breast MRI can provide a sufficient NPV to safely rule out malignancy in mammographic BIRADS 3 lesions.

Materials and methods: In a 3-years consecutive mammographic examination study 176 out of 4391 patients had a lesion classified as BIRADS 3. 76 out of 176 patients underwent breast MRI as diagnostic work-up. Lesions which MRI classified as BIRADS 1 or 2 were considered negative for malignancy. Sensitivity, specificity, PPV and NPV were calculated.

Results: In 27 out of 76 (35.5%) patients MRI showed no enhancement and was classified as BIRADS 1. In 25 (32.9%) patients MRI showed focal or mass enhancement classified as BIRADS 2. In these 52 (68.4%) patients no malignancy was found during at least 2 years study follow-up. The other 24 (31.6%) patients had a lesion classified as BIRADS≥3. Thirteen of these 24 lesions were malignant by pathology. MRI had a sensitivity of 100% (95% CI: 75-100%), specificity of 82.5% (95% CI: 71-91%), PPV of 54.2% (95% CI: 33-74%) and NPV of 100% (95% CI: 93-100%).

Conclusions: Breast MRI should be used in a diagnostic strategy for the work-up of noncalcified BIRADS 3 lesions. Malignancy is ruled out with a very high level of confidence in the majority of patients (68%), herewith avoiding invasive diagnostic procedures.

Introduction

Diagnostic mammography is commonly used to identify possible breast cancers in women and is the primary imaging modality for the early detection of breast cancer. However, mammography has its limitations with regard to both sensitivity (65.6-85.5%) and specificity (87.7-94.3%), which are depended on age and breast density [1,2]. Mammograms are coded using the ordered categories of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BIRADS) lexicon: category 1: negative; 2: benign finding; 3: probably benign; 4: suspicious finding; 5: highly suggestive of malignancy [3]. The diagnostic work-up of breast lesions depends on the BIRADS classification of the breast lesions. The guideline for non-invasive diagnostic tests for breast abnormalities of the Agency for Health Care Research and Quality in the United States (AHRQ) and the guideline of the National Breast Cancer Consultation in the Netherlands (NABON) state that breast lesions classified as BIRADS 1 and 2 require no further diagnostic work-up or follow-up other than routinely required. The work-up for a BIRADS 4 or BIRADS 5 lesion demands a biopsy procedure, because the chance of malignancy for a BIRADS 4 lesion varies from 2% to 95% and for a BIRADS 5 lesion higher than 95% [4,5]. The probability of a BIRADS 3 lesion to be malignant is considered to be less than 2%. Therefore, the work-up of a BIRADS 3 lesion can be a biopsy or follow-up mammography after six months. In practice, the work-up of BIRADS 3 lesions is decided on the possibilities for biopsy procedures, but also on the wish of the patient and the preference of the clinician. Because of the low predictive value of both physical examination and mammography, a large majority of patients referred for biopsy have a benign lesion [6,7].

Breast Magnetic Resonance Imaging (MRI) is emerging as a clinically useful additional diagnostic tool [5,8], but according to AHRQ the additional value of breast MRI in BIRADS 3 lesion is not yet clear [4,5]. There are sparse data available to support the use of breast MRI as problem solving modality in mammographic BIRADS 3 lesions [9,10] and therefore it has not been implemented in common practice. However, breast MRI has the highest overall sensitivity, which usually exceeds 90% [11-13], of all imaging techniques.

In selected populations a negative breast MRI shows a sufficient high negative predictive value (NPV: 91.7-100%) to safely exclude malignancy [9,10,14,15].

The purpose of this study is to determine whether breast MRI can be used as a problem solving modality for mammographic BIRADS 3 lesions by providing a sufficient negative predictive value (>98%) for early work-up and there by safely rule out malignancy and to decrease the percentages of invasive procedures.

Materials and Methods

Patient population

Patients, referred with clinical suspicious for breast cancer, were included consecutively from January 2005 until January 2008 at the University Medical Center Groningen (UMCG). 4391 patients underwent a mammographic examination and diagnostic work-up at the department of radiology.

Over this period in 188 patients mammograms were classified as BIRADS 3 (Table 1).

Table 1 Mammographic BIRADS classification (2005-2008).

BIRADS category	Number of mammography examination
0 need additional imaging evaluation	7 (0.2)
1 negative	89 (2.0)
2 benign finding	3884 (88.4)
3 probably benign	188 (4.3)
4 suspicious abnormality	112 (2.6)
5 highly suggestive of malignancy	111 (2.5)
Total	4391(100)

Note. Values in parentheses are percentage.

Twelve women were excluded: 10 patients did not have a work-up in the UMCG and 2 patients died of cardiovascular disease before study follow-up was done. Seventy-six out of 176 patients with a mean age of 52 years (range, 30-73 years) underwent a breast MRI as

diagnostic work-up of the BIRADS 3 lesion. The final diagnosis was confirmed by pathology or a clinical and diagnostic follow-up of at least 2 years. The remaining 100 patients underwent different work-up strategies (biopsy procedure, surgical intervention, follow-up mammogram or ultrasound) (Fig.1). This study was approved by the Medical Ethical Committee of the University of Groningen.

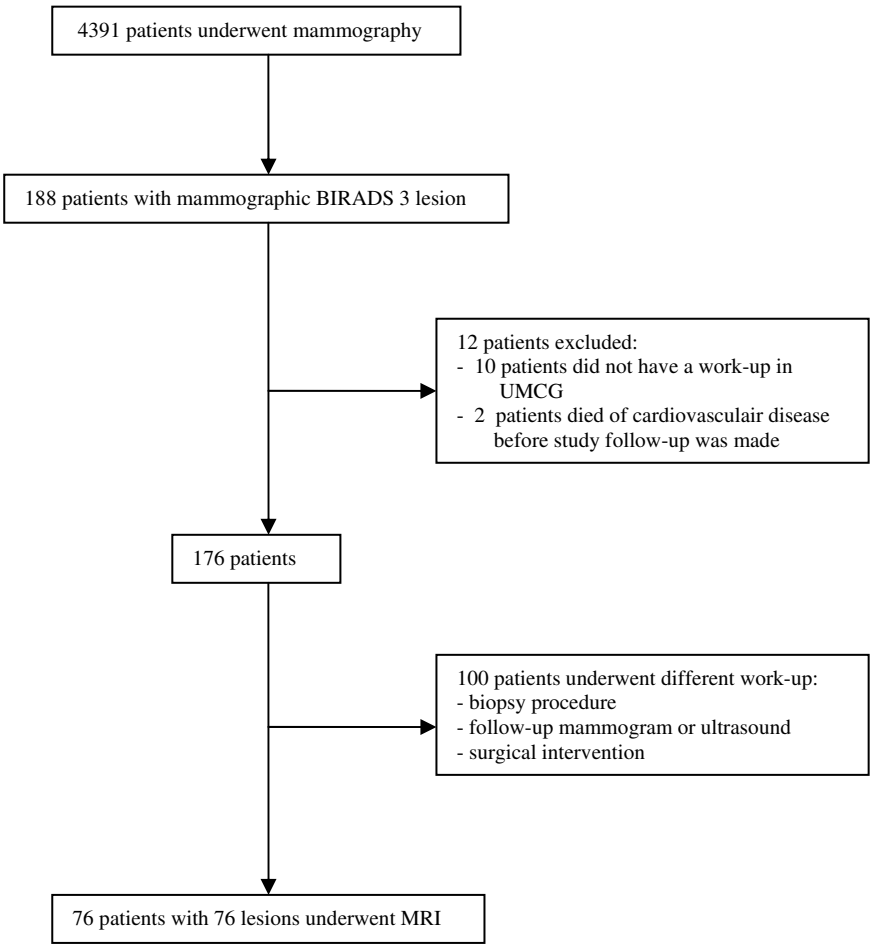

Fig. 1 Flow chart of patient inclusion and with reasons for exclusion.

Mammography

Mammography was obtained on a mammomat Novation system with a Selenium detector (Siemens Medical Solutions, Erlangen, Germany). In all cases, at least standard mammography was performed in craniocaudal and mediolateral oblique views. The radiologist coded the mammograms by using the ordered categories of the ACR BIRADS lexicon (3). All imaging examinations were assessed by 3 breast radiologists, with at least 10-20 years experience in breast imaging.

MRI

MR scans were obtained on a 1.5 Tesla whole body MR scanner (Avanto; Siemens Medical Solutions, Erlangen, Germany) using a dedicated bilateral breast coil with the patient in prone position. In cases of premenopausal women, the MRI was performed in the second week of the menstrual cycle. The standard MRI protocol included a T2 Turbo Spin Echo (TR/TE 4500/102ms, FOV 340mm and slice thickness 4mm) in the transversal plane. A T1 weighted three-dimensional (3D) fast low-angle shot (FLASH) sequence (TR/TE/FA 7.5ms/4ms/25deg, FOV 320mm and slice thickness 1.50mm, totally 1.08min) in the coronal plane was made before and 6 times after Gd intravenous contrast agent (0.2mmol/kg Dotarem) administration. The contrast-enhanced dynamic sequence was performed approximately 30 seconds after injection and was followed by 5 additional consecutive sequences. The total duration of the dynamic study was approximately 8 minutes. Subtracted images were obtained by subtracting pre-contrast images from the post-contrast images using the machines commercially available software. The protocol also included a T1-3D FLASH water excitation (TR/TE/FA 11ms/3.93ms/25deg, FOV 350mm, slice thickness 0.90mm) in the transversal plane. MRI scans were coded using the ordered categories of the ACR BIRADS lexicon [3]. All imaging examinations were assessed by 2 breast radiologists, with at least 10 years experience in breast imaging.

Image and data analysis

Demography and indication for mammography were obtained from the patient records. In each case the category of findings for which the breast MRI was recommended was

analyzed. The mammographic BIRADS 3 findings were noncalcified solid masses, asymmetric densities and microcalcifications [16].

The MR images were classified as normal if no enhancement was seen in the expected location of the mammographic finding (BIRADS 1) or only homogeneous or stippled enhancement was found in the breast, representing normal enhancing breast parenchyma or fibrocystic changes (BIRADS 2). The lesions which were detected on the MRI and corresponded with the area to the mammographic finding were classified as focus, mass enhancement or non-mass enhancement. From the enhancing lesion the location, lesion type, shape, border, distribution, internal enhancement and kinetic curves according to the BIRADS lexicon were assessed and the lesions were classified as BIRADS 3, 4 or 5 [3].

Statistical methods

Lesions which MRI classified as BIRADS 1 or 2 were considered negative for malignancy. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated on the basis of final pathology reports or long-term clinical and diagnostic follow-up findings of at least 2 years. The 95% confidence intervals (CI) were calculated using the binomial distribution. Receiver operating characteristics (ROC) analysis was used to quantify the diagnostic accuracy of MRI for the assessment of mammographic BIRADS 3 lesions. Data were analyzed in STATA SE version 11.0 (STATA, College Station, TX.) and SPSS (SPSS 16.0 for Windows, SPSS Inc.).

Results

Mammographic and MRI findings

The 76 mammographic BIRADS 3 findings were assessed as a noncalcified solid mass (n=56, 73.7%), asymmetric density (n=12, 15.8%) or microcalcifications (n=8, 10.5%) (Table 2).

In 37 (66.1%) out of 56 mammographic noncalcified solid masses MRI showed an enhancement. These 37 enhancements were foci in 22 (59.5%) patients, mass enhancement in 14 (37.8%) patients and non-mass enhancement in 1 (2.7%) patient. Nineteen (33.9%) mammographic noncalcified solid masses showed no abnormal enhancement on MRI.

In 9 (75%) out of 12 mammographic asymmetric densities were assessed by MRI as foci in 4 (33.3%) patients and as mass enhancement in 5 (41.7%) patients. Three (25.0%) patients had no abnormal enhancement on MRI.

In 5 (62.5%) out of 8 mammographic microcalcifications there was no abnormal enhancement seen on the MRI. Three (37.5%) patients with microcalcifications had a mass enhancement on the MRI (Table 3).

Table 2 Mammographic BIRADS 3 findings.

Mammographic BIRADS 3 findings	Number
Noncalcified solid mass	56 (73.7)
Asymmetric density	12 (15.8)
Microcalcifications	8 (10.5)
Total	76 (100)

Note. Values in parentheses are percentage.

Table 3 Mammographic BIRADS 3 findings and MRI findings.

	MRI findings			
	No abnormal enhancement	Foci	Mass enhancement	Non-mass enhancement
Mammographic BIRADS 3 findings				
Noncalcified solid mass (n=56)	19	22	14	1
Asymmetric density (n=12)	3	4	5	0
Microcalcifications (n=8)	5	0	3	0
Total	27 (35.5)	26 (34.2)	22 (29.0)	1 (1.3)

Note. Values in parentheses are percentage.

MRI BIRADS category

In 27 (35.5%) out of 76 patients the breast MRI showed no abnormal enhancement in the area corresponding to the mammographic finding and was classified as BIRADS 1. In these patients no malignant lesion was seen during at least 2 years study follow-up.

In 26 (34.2%) out of 76 patients the MRI showed foci in the breast which were classified as BIRADS 2 in 21 (80.8%) patients and as BIRADS 3 in 4 (15.4%) patients. The study follow-up or pathology of these patients showed no malignancy. In one (3.8%) patient the focus was classified as BIRADS 4. This patient had a surgical excision which showed normal fibroglandular tissue with pathology.

Twenty-two (28.9%) patients had a mass enhancement on the MRI. The mass enhancements were classified as BIRADS 2 in 4 (18.2%) patients, as BIRADS 3 in 8 (36.4%) patients, as BIRADS 4 in 5 (22.7%) patients and as BIRADS 5 in 5 (22.7%) patients. The 4 BIRADS 2 lesions and 6 out of the 8 BIRADS 3 lesions showed no malignancy by study follow-up or pathology. The other masses were malignant by pathology.

In only 1 (1.3%) patient a non-mass enhancement was detected on the MRI. This non-mass enhancement was classified as BIRADS 4 and pathology confirmed malignancy (Table 4).

Table 4 MRI BIRADS classification and pathologic proven breast cancer.

	MRI BIRADS category									
	1 (n=27)		2 (n=25)		3 (n=12)		4 (n=7)		5 (n=5)	
Number of breast cancer	-	+	-	+	-	+	-	+	-	+
MRI findings										
No abnormal enhanc. (n=27)	27	0								
Foci (n=26)			21	0	4	0	1	0		
Mass enhancement (n=22)			4	0	6	2	0	5	0	5
Non-mass enhancement (n=1)							0	1		
Total	27	0	25	0	10	2	1	6	0	5

The breast MRI had a sensitivity of 100% (95% CI: 75-100%), specificity of 82.5% (95% CI: 71-91%), PPV of 54.2% (95% CI: 33-74%) and NPV of 100% (95% CI: 93-100%). ROC analysis revealed an area under the curve (AUC) of 0.98±0.03 (95% CI: 0.85-0.98) for breast MRI in the differentiation between benign and malignant mammographic BIRADS 3 lesions (Fig. 2).

Thirteen (17.1%) out of the 76 mammographic BIRADS 3 lesions were malignant.

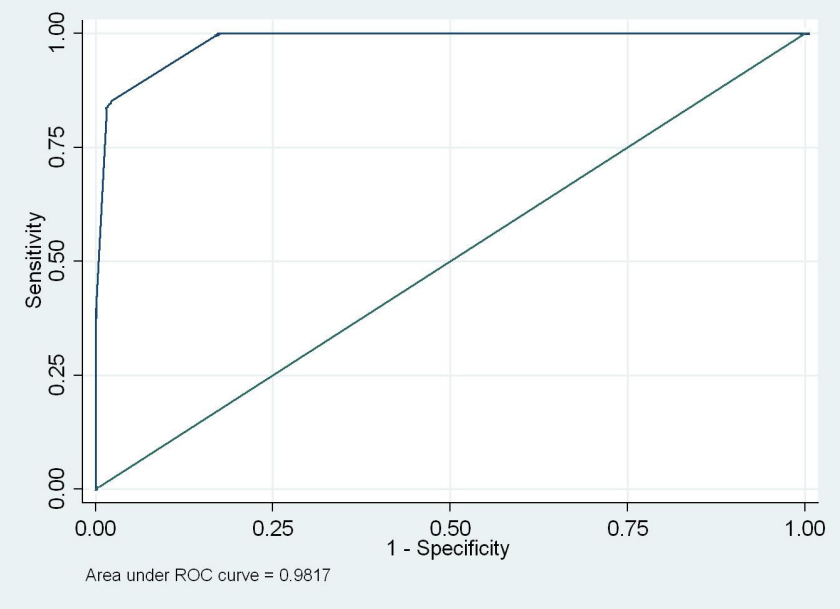

Fig. 2 ROC curve for the accuracy of breast MRI to rule out malignancy in mammographic BIRADS 3 lesions.

Pathology

In 24 (31.6%) out of 76 patients the final diagnosis was based upon pathology findings of the specimen. Eighteen (75.0%) patients underwent a biopsy procedure and 6 (25.0%) patients a surgical intervention after the MRI scan. Ten (41.7%) out of these 24 patients had invasive ductal carcinoma, 2 (8.2%) patients had an invasive lobular carcinoma and 1

(4.2%) patient had a metaplastic carcinoma. Normal fibroglandular tissue was found in 10 (41.7%) patients and a lipoma was found in 1 (4.2%) patient.
Fifty-two (68.4%) out of 76 patients had a study follow-up of at least 2 years. In these patients no malignant tumor was detected.

Discussion

According to the guideline of AHRQ and NABON the diagnostic work-up of mammographic BIRADS 3 lesions should be a biopsy or a follow-up mammography after 6 months [4,5]. In our study, we established that there is a role for breast MRI in mammographic BIRADS 3 lesions, because a non-invasive imaging modality with high NPV can lower the percentage of invasive procedures. The accuracy of the MRI in our study is excellent (AUC=0.98) and the NPV is near to 100% (95% CI: 93-100%). Therefore, further diagnostic work-up is not needed in patients with a breast MRI classified as BIRADS 1 or 2. In our study this is 68.4% (52/76) of the patient group. To our knowledge there is only one other report published which deals with the role of MRI in the evaluation of probably benign lesions (BIRADS 3) in mammography [9]. In this publication a NPV of 100% was reported [9]. Furthermore, other single-center studies, which characterize breast lesions independent on BIRADS classification with MRI, have shown that the NPVs of breast MRI have been as high as 97% [10,14,15].
Kuhl [8] on the other hand described that the evidence for the effectiveness of breast MRI is relatively weak in helping to solve mammographic interpretations problems, because in a multicenter trial of Bluemke et al. the NPV is not high enough to exclude malignancy with sufficient confidence in case of an equivocal or suspicious lesion seen at conventional imaging [11]. The diagnostic accuracy of MRI was studied in 821 patients with a suspicious (BIRADS 4 or 5) mammographic finding (85%) or a suspicious clinical finding with a negative or benign conventional work-up (15%) prior to biopsy [11]. MRI had a negative predictive value of 85% with cancer missed in 48 of 329 negative MRI examinations. Therefore, a biopsy of suspicious mammographic findings (BIRADS 4 or 5) or clinical findings based on the absence of a suspicious MRI correlate can not be avoided [11]. However, this widely referenced multicenter study was performed in 14 hospitals from

1998 to 2001 and therefore used now outdated MR equipment. Furthermore, Bluemke et al. [11] included microcalcifications of the breast which have negative influence on the NPV. There are 3 studies [17-19] which investigated the role of breast MRI in microcalcifications. The NPV of these studies varies between 76% and 97% which is in accordance with Bluemke results. In our study only 8 patients with mammographic BIRADS 3 microcalcifications underwent MRI. If the MRI showed no abnormal enhancement no malignant lesion were detected by stereotactic biopsy or 2 years study follow-up. However, a definitive conclusion cannot be drawn because our group of microcalcifications is too small.

For mammographic BIRADS 3 lesions it is difficult to decide which work-up strategy (biopsy or follow-up after 6 months) is suitable and thus depending on the preference of the clinician and the wish of the patient. Therefore, in this group it can be expected that MRI has an additional value.

The majority of mammographic BIRADS 3 findings in our study were noncalcified solid masses and asymmetric densities. When these mammographic lesions in our study showed no abnormality or foci (lesions smaller than 5 mm) on the MRI, malignancy could be excluded. This was in accordance with the publication of Gokalp et al. [9] and Moy et al. [10]. In the report of Gokalp 85% of the 56 mammographic BIRADS 3 lesions were noncalcified shaped lesions or asymmetric densitities which were correctly classified as benign [9].

In the study of Moy et al. [10] 115 breasts MRI's were used as adjunctive tool and the findings were correlated with pathology. The equivocal mammographic findings for which MRI was performed were asymmetry without associated microcalcifications (85.2%), architectural distortion (10.4%) and change in the appearance of the site of a previous benign biopsy finding (4.3%). MRI had a sensitivity of 100%, specificity of 91.7%, NPV of 100%, PPV of 40.0% and overall accuracy of 92.2%. Moy et al. concluded that breast MRI could be an useful adjunctive tool when equivocal findings at conventional mammography are asymmetry or architectural distortion [10].

In our study the chance of malignancy in the mammographic BIRADS 3 lesions is approximately 17%. This is considerably higher than is stated in the guideline of AHRQ and NABON (< 2%) [4,5]. It is not likely that the high percentage of malignancy is due to

the selection of lesions for MRI. Taken into account the total group of 176 BIRADS 3 lesions, also 17.6% (n=31) of 176 breast lesions were malignant. This result confirms that classifying lesions in the BIRADS category 3 is difficult with a very high inter- and intraobserver variability in interpretation of mammographic features [20]. Therefore, breast MRI can be helpful in cases of mammographic BIRADS 3 lesions. MRI not only has shown to give near to 100% (95% CI: 93-100%) prediction of benign lesions, which means that no further invasive diagnostic work-up is needed, it also gives a better prediction of malignant lesions assessed as BIRADS 3 on mammogram.

In conclusion, MRI can be used as problem solving modality in noncalcified BIRADS 3 lesions, because the NPV of MRI is high enough to rule out malignancy with sufficient confidence. When the MRI is assessed as BIRADS 1 or 2, no further invasive diagnostic assessment is needed. Further multicenter research is needed to verify and implement these results in regular care.

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Chapter 4

Computer-aided detection in breast MRI: a systematic review and meta-analysis

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Abstract

Objectives: To evaluate the additional value of computer-aided detection (CAD) in breast MRI by assessing radiologists' accuracy in discriminating benign from malignant breast lesions.

Methods: A literature search was performed with inclusion of relevant studies using a commercially available CAD system with automatic colour mapping. Two independent researchers assessed the quality of the studies. The accuracy of the radiologists' performance with and without CAD was presented as pooled sensitivity and specificity.

Results: Of 587 articles, 10 met the inclusion criteria, all of good methodological quality. Experienced radiologists reached comparable pooled sensitivity and specificity before and after using CAD (sensitivity: without CAD: 89%; 95% CI: 78-94%, with CAD: 89%; 95%CI: 81-94%) (specificity: without CAD: 86%; 95% CI: 79-91%, with CAD: 82%; 95% CI: 76-87%). For residents the pooled sensitivity increased from 72% (95% CI: 62-81%) without CAD to 89% (95% CI: 80-94%) with CAD, however, not significantly. Concerning specificity, the results were similar (without CAD: 79%; 95% CI: 69-86%, with CAD: 78%; 95% CI: 69-84%).

Conclusions: CAD in breast MRI has little influence on the sensitivity and specificity of experienced radiologists and therefore their interpretation remains essential. However, residents or inexperienced radiologists seem to benefit from CAD concerning breast MRI evaluation.

Introduction

Dynamic contrast-enhanced Magnetic Resonance Imaging (MRI) is increasingly used to evaluate pathological features of the breast. Applications for MRI of the breast include diagnostic and screening indications [1-6]. Image analysis is based on the enhancement pattern of lesions in dynamic breast MRI and on morphological characteristics [7-9]. Using those two criteria for the interpretation of the images, breast MRI has a very high sensitivity, which usually exceeds 90% [10-12] and a negative breast MRI shows a sufficient high negative predictive value (NPV) (97%) to safely rule out malignancy [13-15]. However, breast MRI has several limitations, the overall reported specificity varies between 67% and 72%, which therefore results in a high number of false-positive results [10,12,16]. Furthermore, MRI requires significant time for image acquisition, processing and interpretation [17,18]. In order to try to overcome those limitations, Computer Aided Detection (CAD) programs for MR imaging of the breast have been developed [18]. In general, CAD software was developed to identify suspect features on the image and bring them to the attention of the radiologist, in order to decrease false-negative readings [19]. However, in breast MRI, most lesions were regarded as having already been detected by the radiologist. Therefore, the primary aim to develop CAD for breast MRI was not to identify lesions, but to assist the radiologist in determining which lesions are benign and which are malignant.

Computer-aided detection systems automate many processing and analysis functions, which would normally have to be performed manually by MRI technologists and radiologists. The automated kinetic assessment of CAD generates a colour-coding based on the signal intensity voxel changes during the enhancement of the breast tissue. This provides an easier way of interpreting the patterns of contrast enhancement (persistent, plateau and washout enhancement) across a series of images, which may help identify lesions and their likelihood of being malignant.

The implementation of CAD software may improve the accuracy of breast MRI by reducing the number of false-positive diagnoses and by shortening the time needed to interpret breast MRI images [17,18,20,21]. Furthermore, a state of the art CAD system should automatically identify (almost) all non-calcified lesions suspected of malignancy at

mammography. This is reflected by a very high sensitivity and NPV for these non-calcified breast lesions.

The purpose of this systematic review and meta-analysis is to assess the radiologists' accuracy in discriminating benign from malignant breast lesions regarding breast MRI with and without CAD implementation in terms of sensitivity and specificity.

Materials and Methods

Search strategy

A computerised search was performed to identify all relevant studies in Medline and Embase up to 2010. The following search terms were used in Medline: "Diagnosis, Computer-Assisted" [Mesh term] OR "computer-aided-diagnosis" [Text Word] OR "computer-aided-detection" [Text Word] OR "computer-aided" [Text Word] OR "CAD" [Text Word] OR "three-time-point method" [Text Word] AND "Magnetic Resonance Imaging" [Mesh term] OR "Magnetic Resonance Imaging" [Text Word] OR "MRI" [Text Word] OR "MR imaging" [Text Word] AND "Breast Neoplasms" [Mesh term] OR "breast cancer" [Text Word] OR "mamma carcinoma" [Text Word] OR "malignant breast lesions" [Text Word] AND "Sensitivity and Specificity" [Mesh term] OR "specificity OR sensitivity" [Text Word]. In Embase the same strategy was used. All languages were considered.

Eligibility criteria and study selection

We searched for studies assessing the value of CAD for a radiologist in the discrimination between benign and malignant breast lesions with MRI. Studies were included if the following inclusion criteria were met: (1) all patients had undergone breast MRI; (2) a commercially available CAD system was used; (3) the study population had benign and malignant breast lesions; (4) accuracy, sensitivity, specificity, positive predictive value and/or negative predictive value was/were measured or could be derived, and (5) studies had to be published with original data in peer-reviewed journals. Studies in which an institution-specific CAD system was used were excluded, as well as reviews, editorials and case reports.

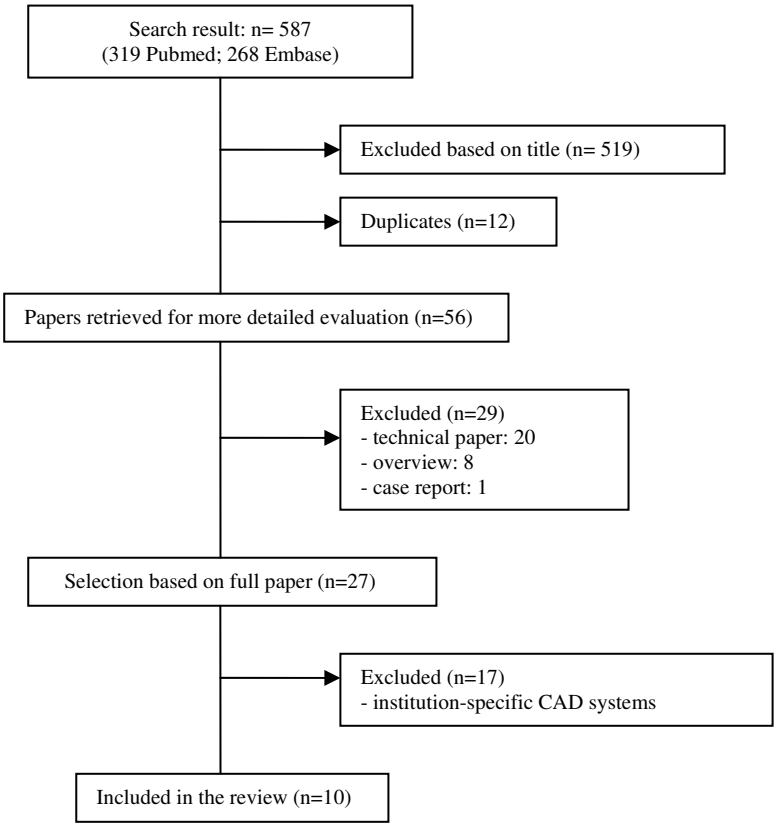

Fig. 1 Flow chart of search results, with reasons for exclusion and the total number of studies included.

Two researchers (MDD, MCJW) independently selected relevant studies based on title and abstract or full article. Any discrepancies concerning the study selection were resolved by discussion of the full article. The complete search yielded 587 studies. 519 out of 587 studies were excluded based on the title. After removing duplicates (n=12), 56 studies were screened on title and abstract. Twenty-nine studies did not meet the inclusion criteria (technical article (n=20), overview (n=8) and case report (n=1)). From the remaining 27 studies the full article was reviewed. Seventeen studies were excluded because CAD was an institution-specific CAD system. Ten studies [20-29] fulfilled our inclusion criteria (Fig. 1). Eight studies were in the English language [20-24,26,27,29]; the other 2 were in the German Language [25,28].

Data collection and quality assessment

The following study descriptives were extracted: population descriptives (age, number of patients, number of benign and malignant lesions), study design, type of MRI used, type of CAD software used, minimum threshold enhancement used, number of radiologists that assessed the MR images with and without the use of CAD and diagnostic accuracy numbers (true-positives, false-positives, true-negatives and false-negatives).

Study quality was assessed independently by the same two observers using the QUADAS tool [30,31], disagreement was resolved by arbitration. This evidence-based tool is developed specifically to assess the quality of diagnostic accuracy studies and includes 14 quality items. The 14 items can be scored as "yes", "no" or "unclear". The total score can range from 0 to 14, in which 14 is the maximum attainable score.

Statistical analysis

The performance of the radiologist in distinguishing breast lesions on MRI with and without the implementation of CAD was assessed. Besides the use of CAD, comparisons were made between radiologists with experience in imaging assessment and residents or radiologists with no or minor experience. Primary outcome was sensitivity and specificity at tumour level. Pooling of data was performed within the bivariate mixed-effects binary regression modelling framework. Model specification, estimation and prediction were carried out with xtmelogit in STATA. Using the model summary sensitivity and specificity were calculated, and a summary ROC curve was drawn (with AUC and confidence intervals). A forest plot was generated containing the individual study sensitivities and specificities with 95% confidence intervals (CI) and the pooled sensitivity and specificity estimates.

A test for heterogeneity was applied, using the I^2 statistic [32]. This statistic calculates the percentage of total variation across studies that can be attributed to inter-study heterogeneity, ranging from 0 (no heterogeneity) to 100% (all variance due to heterogeneity). The presence of publication bias was visually assessed by producing a funnel plot. In STATA linear regression was performed of log odds ratios on the inverse root of effective sample sizes as a test for funnel plot asymmetry. The log odds ratios are defined as the log transformed diagnostic odds ratios, which are needed for the performance

of linear regression. Publication bias was considered present if there was a significant non-zero slope coefficient, ($p < 0.10$), suggesting that only the small studies reporting a high sensitivity with CAD had been published, whereas the small studies reporting a lower sensitivity had not been published. Data were analysed in SPSS 16.0 (SPSS, Chicago, IL, USA), Meta Disc [33] and STATA SE version 11.0 (STATA, College Station, TX, USA).

Results

Study descriptives

The 10 studies included a total of 895 patients (range 29-329) with a total of 1264 breast lesions (range 33-469) of which 606 were classified as malignant (range 9-279) and 658 as benign (range 22-190) [20-29].

In 5 [23,24,26-28] studies a selection was made of patients with suspect findings based on mammography and ultrasound examinations. In the other 5 studies [20-22,25,29] patients with a suspect lesion on MRI were included. One of these 5 studies retrospectively searched the database of an ongoing MRI screening study of patients at high risk of breast cancer for BIRADS 3-5 lesions that were detected with MRI [22], and 2 studies included lesions that were not palpable and were not visible on mammography or ultrasound [20,21]. In all 10 studies histology was used as the gold standard. In 4 studies a follow-up MRI after 6 or 24 months was performed [23,25,28,29]; in the case of positive findings biopsy provided further histological assessment.

Mean study quality was 12.6, ranging from 10 to 14. Four studies were of maximum quality (Table 1) [20,21,26,27].

CAD systems

In all 10 studies the CAD systems (CADstream, DynaCAD, Fulltime point, 3-Time-Point Method and CAD-Gaea) incorporated precontrast medium (unenhanced) images and 2 (immediate and delayed) or all postcontrast medium (enhanced) images [20-29]. The CAD systems compared pixel intensity values on the precontrast medium and immediated postcontrast medium series. If a pixel value increased above a user-specified minimum enhancement threshold, such as a 50 or 100% increase in enhancement, the pixel was

Table 1 Study characteristics of the 10 included studies (*SD* standard deviation, *NR* not reported, *P* prospective, *R* retrospective, *c* consecutive, *TB* tumour-based).

Study (author, ref., year of publication)	No. of patients	Study design	Quality score	Mean age (SD or range)	No. of lesions	No. of malignant	No. of benign	Type of analysis	MRI	CAD system
Arazi [22] 2009	53	R, c	13	47 (26-68)	56	22	34	TB	1.5T	CAD-Gaea
Meeuwis [27] 2009	65	R, c	14	49 (29-71)	71	49	22	TB	3.0T	CADstream
Baltzer [23] 2009	51	R, c	12	51 (13)	90	46	44	TB	1.5T	DynaCAD
Baltzer [24] 2009	329	P, c	13	53 (15-83)	469	279	190	TB	1.5T	DynaCAD
Veltman [29] 2009	NR	R,c	11	NR	52	25	27	TB	1.5T	3-Time-Point
Renz [28] 2008	48	P, c	11	51 (31)	88	43	45	TB	1.5T	DynaCAD Full-time point
Hauth [25] 2008	137	R	10	NR	183	61	122	TB	1.5T	3-Time-Point
Williams [21] 2006	126	R, c	14	52 (27-86)	154	41	113	TB	1.5T	CADstream
Lehman [20] 2005	29	R, c	14	NR	33	9	24	TB	1.5T	CADstream
Kelcz [26] 2002	57	P, c	14	52 (31-80)	68	31	37	TB	1.5T	3-Time-Point

regarded as meeting threshold enhancement. Once a pixel was identified as enhancing above the established threshold, the CAD systems compared pixel signal intensity values on the immediate and delayed postcontrast medium series to indicate washout enhancement, plateau enhancement or persistent enhancement. A specific colour or colour intensity was assigned to each pixel for different types of tissue enhancement. The end result of all CAD systems was a colour overlay on each MRI slice indicating regions of significant enhancement and providing details about enhancement type and extent.

CAD threshold enhancement

Six [20-24,27] studies analysed the presence or absence of "threshold enhancement" at different minimum thresholds. Lehman et al. [20], Williams et al. [21] and Meeuwis et al. [27] used the CAD system CADstream. The sensitivity at the minimum thresholds of 50, 80% and 100% remained the same. The specificity increased at higher minimum thresholds. The study by Meeuwis et al. [27] showed a higher specificity than the other two studies. In the studies by Baltzer et al. [23,24] DynaCAD was used. In these studies, the

Table 2 The sensitivity and specificity of a CAD system using the presence or absence of lesion enhancement at the user-specified minimum thresholds.

Study	MRI	CAD system	No. of lesions	MRI assessed by using	Sensitivity	Specificity
Arazi [22]	1.5T	CAD-Gaea	56	Threshold 50%	100%	0%
				Threshold 80%	95.5%	14.7%
				Threshold 100%	72.7%	44.1%
Baltzer [23]	1.5T	DynaCAD	90	Threshold < 50%	100%	0%
				Threshold 50%-100%	84.8%	45.4%
				Threshold > 100%	52.1%	72.7%
Baltzer [24]	1.5T	DynaCAD	469	Threshold < 50%	100%	0%
				Threshold 50%-100%	86.4%	53.2%
				Threshold > 100%	52.0%	83.7%
Meeuwis [27]	3.0T	CADstream	71	Threshold 50%	97.9%	86.4%
				Threshold 100%	97.9%	90.9%
Williams [21]	1.5T	CADstream	154	Threshold 50%	92.7%	8.9%
				Threshold 100%	92.7%	23.0%
Lehman [20]	1.5T	CADstream	33	Threshold 50%	100%	25.0%
				Threshold 80%	100%	33.0%
				Threshold 100%	100%	50.0%

Table 3 The performance of radiologists and residents in breast MRI diagnosis in terms of sensitivity and specificity with and without the use of a CAD system, specified for type of CAD and MRI system, number of lesions, and experience (*RAD* radiologist *RES* resident).

Study	MRI	CAD system	No. of lesions	MRI assessed by using	Experience	Sensitivity	Specificity
Arazi [22]	1.5T	CAD-Gaea	56	CAD+RAD	5 years	73.0%	56.0%
Meeuwis [27]	3.0T	CADstream	71	CAD+RAD1	> 5 years	88.5%	75.0%
			71	CAD+RAD2	> 5 years	92.3%	87.5%
			71	CAD+RES1	6 months	88.5%	93.8%
			71	CAD+RES2	0 months	84.6%	81.3%
			42	RAD (manual)[a]		84.6%	68.8%
Baltzer [23]	1.5T	DynaCAD	90	CAD+RAD	1-3 years	80.4%	72.7%
Baltzer [24]	1.5T	DynaCAD	469	CAD+RAD	>300 MRIs	78.8%	73.2%
			469	RAD (manual)[a]		75.3%	76.3%
			469	RAD (visual)[b]		72.4%	77.4%
Renz [28]	1.5T	DynaCAD	88	CAD+RAD1	> 500 MRIs	100%	86.7%
			88	CAD+RAD2	> 500 MRIs	95.3%	93.3%
			88	CAD+RAD3	< 50 MRIs	90.7%	73.3%
		Full-time point	88	CAD+RAD1		100%	84.4%
			88	CAD+RAD2		95.3%	91.1%
			88	CAD+RAD3		100%	66.7%
			88	RAD1 (visual)[b]		97.7%	84.4%
			88	RAD2 (visual)[b]		93.0%	93.3%
			88	RAD3 (visual)[b]		86.0%	77.8%
Veltman [29]	1.5T	3-Time-point	52	CAD+RES1	0 months	80%	78%
			52	CAD+RES2	3 months	80%	81%
			52	CAD+RES3	5 years	80%	85%
			52	CAD+RAD4	15 years	80%	78%
			52	RES1 (manual)[a]		68%	67%
			52	RES2 (manual)[a]		52%	81%
			52	RES3 (manual)[a]		72%	85%
			52	RAD4 (manual)[a]		84%	85%
Hauth [25]	1.5T	3-Time-point	183	CAD+RAD	3 years	60.7%	83.6%
Kelcz [26]	1.5T	3-Time-point	68	CAD+RAD	>500 MRIs	87.0%	84.0%

[a] Manual: manual curve analysis by using the region of interest (ROI) method.
[b] Visual: visual evaluation of contrast enhancement.

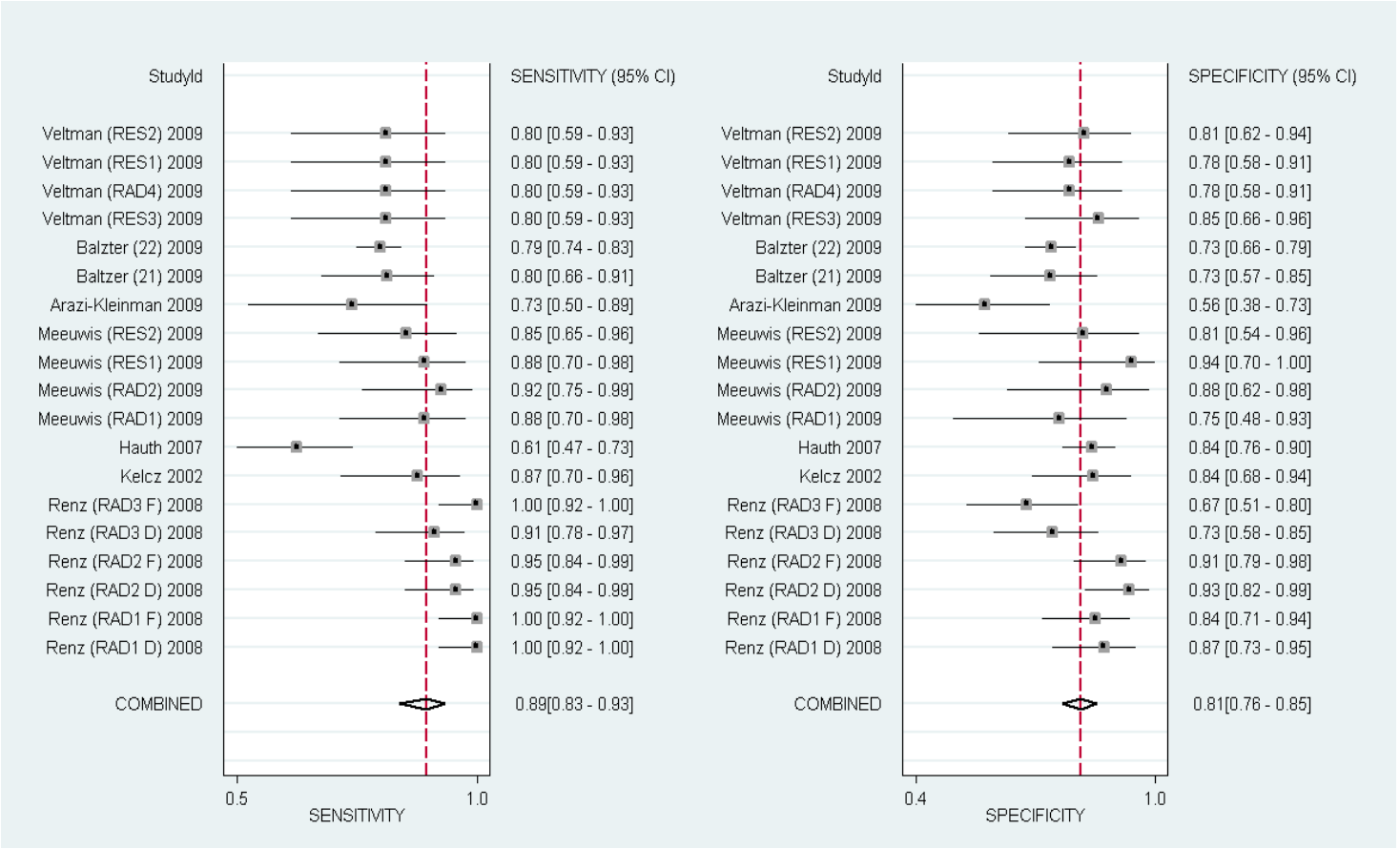

Fig. 2 Forest plot of pooled sensitivity and specificity of radiologists and residents assessing breast lesions on MRI with the use of a CAD system.

sensitivity decreased and the specificity increased at higher minimum thresholds. CAD-Gaea [22] had the same results as DynaCAD with respect to sensitivity and specificity, although CAD-Gaea had a lower level of specificity. Meeuwis et al. [27], using CADstream, reported the highest sensitivity and specificity (Table 2).

Radiologist with or without CAD

In 8 out of 10 studies [22-29] the sensitivity and specificity of the radiologist or resident in assessing MR images with the use of CAD were measured (Table 3). The enhancement thresholds used were set up individually according to the radiologist's preference. Furthermore, in 4 [24,27-29] out of these 8 studies the sensitivity and specificity of the radiologist or resident was also calculated without the use CAD. In these four studies the radiologists or residents assessed the MR images as visual evaluation of contrast enhancement or by making a manual curve analysis by using the region of interest (ROI)

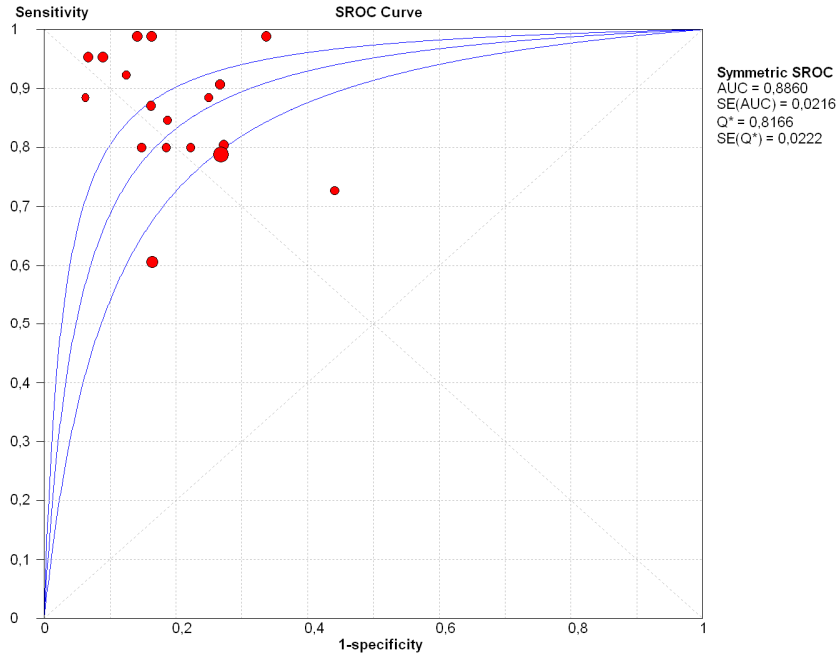

Fig. 3 Summary ROC curve regarding the studies of radiologists and residents using a CAD system.

method [24,27-29]. The pooled sensitivity and specificity of radiologists and residents assessing breast lesions on MRI without the implementation of CAD was 82% (95% CI: 72-90%) and 81% (95% CI: 74-87%), respectively. With CAD implementation they attained higher sensitivity scores (sensitivity: 89%**,** 95% CI: 83-93%; specificity: 81%**,** 95% CI: 76-85%) (Fig. 2). The sROC curve showed an AUC of 0.89 (Fig. 3). In 3 studies differentiation was made between radiologists with experience and residents with no or minimal experience [27-29]. The experience of those radiologists varied from 5 to 15 years (or > 500 MRIs). Residents had no more than 6 months (or < 50 MRIs) breast MRI experience. After stratification, the experienced radiologists showed a comparable pooled sensitivity of 89% with (95% CI: 81-94%) and without (sensitivity: 89%; 95% CI: 78-94%) CAD implementation. The pooled specificity of 86% (95% CI: 79-91%) decreased to 82% (95% CI: 76-87%) with CAD. Residents or radiologists with less experience showed a pooled sensitivity of 72% (95% CI: 62-81%) and a pooled specificity of 79% (95% CI: 69-86%) when assessing breast lesions on MRI without CAD. With the use of CAD, their sensitivity increased to 89% (95% CI: 80-94%), whereas their specificity remained comparable (specificity: 78%; 95% CI: 69-84%) (Table 4).

Table 4 Results of pooled sensitivity and specificity (95% CI) of the radiologist in assessing breast lesions on MRI with and without the use of a CAD system in general, stratified for experienced radiologists and residents with no or less experience (RANDOM effects model).

Outcome or subgroup	Studies[a]	Sensitivity (95% CI)	Specificity (95%CI)
Radiologist no CAD, general	4[b]	82% (72%-90%)	81% (74%-87%)
Radiologist with CAD, general	8[c]	89% (83%-93%)	81% (76%-85%)
Experienced radiologist no CAD	4[b]	89% (78%-94%)	86% (79%-91%)
Experienced radiologist with CAD	8[c]	89% (81%-94%)	82% (76%-87%)
Residents no CAD	3[d]	72% (62%-81%)	79% (69%-86%)
Residents with CAD	3[d]	89% (80%-94%)	78% (69%-84%)

[a] In studies in which more than one radiologist/resident (blinded) assessed the images, the pooled calculation was based on all relevant radiologists in that study.
[b] Meeuwis [27], Baltzer [24], Renz [28], Veltman [29].
[c] Arazi-Kleinmann [22] Meeuwis [27], Baltzer [23], Baltzer [24], Renz [28], Veltman [29], Hauth [25], Kelcz [26].
[d] Meeuwis [27], Renz [28], Veltman [29].

Analyses of heterogeneity

Moderate to substantial heterogeneity was observed among the eight studies exploring the sensitivity and specificity of radiologists assessing MR images with and without the implementation of CAD (sensitivity: no CAD: I^2: 78%, p<0.0001, with CAD: I^2: 80%, p<0.0001; specificity: no CAD: I^2: 46%, p=0.007, with CAD: I^2: 55%, p=0.002). After stratification of radiologists with experience and residents with no or minimal experience, heterogeneity did not change for experienced radiologists (sensitivity: no CAD: I^2: 79%, p<0.0001, with CAD: I^2: 83%, p<0.0001), and residents (sensitivity: no CAD: I^2: 79%, p=0.009; with CAD: I^2: 64%, p=0.02). Concerning specificity, heterogeneity dropped to low to moderate (radiologists without CAD: specificity: I^2: 56%, p=0.04, radiologists with

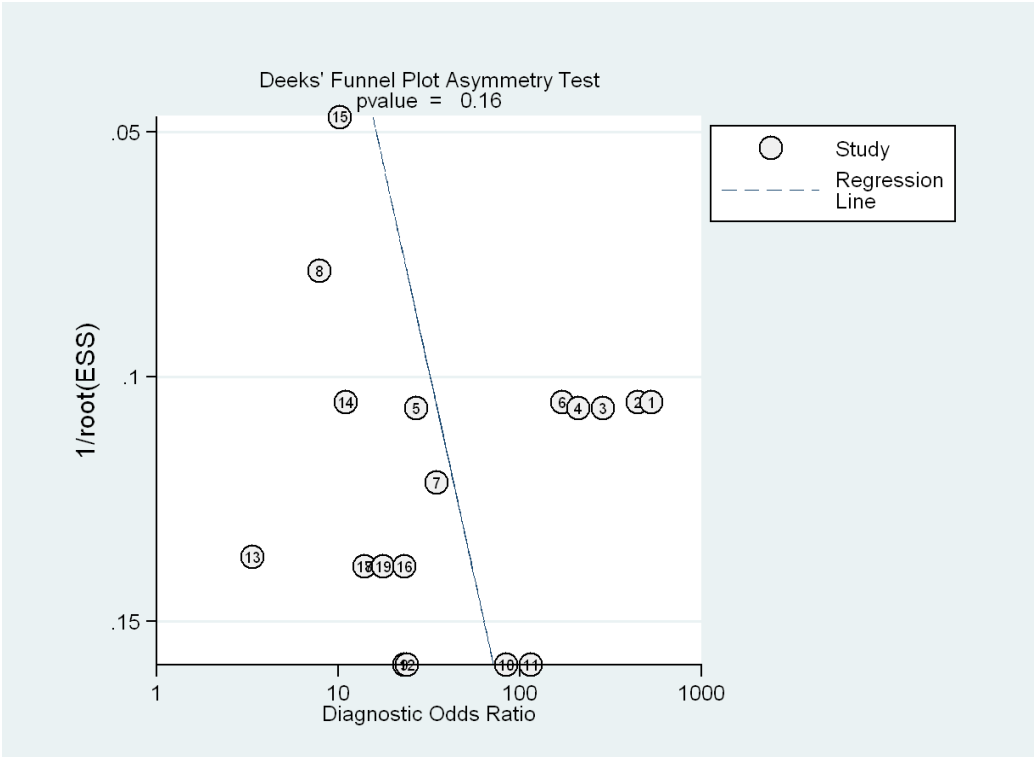

Fig. 4 Funnel plot with log odds ratios on the inverse root of effective sample sizes for visualisation of publication bias.

CAD: specificity: I^2: 62%, p=0.01; residents without CAD: specificity: I^2: 33%, p=0.22; residents with CAD: specificity: I^2: 24%, p=0.26). Because of heterogeneity and possible unmeasured variance at the study level a random-effects model was used to obtain all pooled estimates, as this model interprets the available data with more caution and uses broad confidence intervals**.**

Assessment publication bias

A non-significant non-zero slope coefficient (p-value = 0.16) indicated that there was no evidence of publication bias (Fig. 4). This suggests that we most likely did not miss studies with a negative outcome.

Discussion

This meta-analysis shows that the pooled sensitivity and specificity of the experienced radiologist for the assessment of breast lesions with MRI remains comparable with the implementation of CAD. Residents or radiologists with less experience seem to attain a higher sensitivity with CAD implementation, although not significant.

All selected studies were of high quality, so it is likely that the quality of the studies did not have a significant impact on the results of the meta-analysis. Furthermore, there was no evidence of publication bias and therefore it is not expected that the meta-analysis overestimates the effect of CAD evaluation.

The ten studies used different indications for breast MRI and there was a wide variation in the number and tissue type of lesions selected [20-29]. This resulted in the greater heterogeneity. Therefore, we used a random-effects model that interprets the results with more caution. Furthermore, there was an indication of selection bias. In all studies the radiologists only assessed MRIs with lesions (≥ BIRADS 2) and discriminated between benign and malignant. This selection increased the prevalence of breast malignancy in the study population compared with the target population. The lesion selection could have influenced the performance of the radiologist.

Six studies analysed the influence of the presence or absence of “threshold enhancement” at different minimum thresholds [20-24,27]. Of those six, the study by Meeuwis et al. [27]

resulted in the highest sensitivity and specificity. This result could be explained by the fact that a 3.0T MRI system was applied, which has a better performance than the 1.5T MRI scanner which was used in the other studies.

With CADstream the sensitivity at a higher enhancement threshold remained the same, i.e. the same malignant lesions enhanced at the 50%, 80% and 100% thresholds [20]. The remaining false-negative enhancing malignant lesions showed no enhancement with CADstream due to a noise filtering process leading to failure of automatic analysis of small areas of enhancement [21,27]. The specificity of CADstream increased at higher enhancement thresholds, which means that at a higher threshold benign lesions did not enhance [20]. Therefore, absence of lesion enhancement at higher thresholds helps to improve the discrimination between benign and malignant lesions. In comparison to the study by Meeuwis et al. [27], the low specificity of the study by Williams et al. [21] is most likely due to the high prevalence (n= 22/71 versus n= 113/154) and the large tissue type variation of benign lesions.

With the DynaCAD software the specificity performance was analogous to that of the CADstream software. The sensitivity of DynaCAD however, decreased at higher threshold enhancements, not visualising all malignant enhancements, resulting in false-negative lesions [23].

Residents or radiologists with no or less experience achieved a higher sensitivity when they were accompanied by a CAD system for discrimination between breast lesions on MRI. The change in sensitivity after using CAD was not significant. Nevertheless, a considerable increase could be seen (sensitivity from 72%; 95% CI: 62-81% to 89%; 95% CI: 80-94%). This increase could be a result of the fact that CAD brings more enhancing lesions to the attention of the resident or inexperienced radiologist. Therefore, it seems that they benefit from CAD when assessing breast lesions with MRI. However, more research must be conducted to verify these results.

The performance of the experienced radiologists showed a non-significant decrease in specificity from 86% (95% CI: 79-91%) without CAD to 82% (95% CI: 76-87%) with CAD. A clarification for this observation could be that CAD systems are only based on the enhancement dynamic, without regarding the morphology of the lesion. As a consequence, the use of CAD could lead to a higher number of enhancing lesions, part of which could be

assigned as benign on the basis of morphology. The experienced radiologists can be mislead by the enhancement pattern of CAD, resulting in a decrease in specificity. Therefore, it is important that experienced radiologists are aware of this.

In conclusion, concerning the assessment of MR images CAD has little influence on the sensitivity and specificity of the performance of radiologists experienced in breast MRI diagnosis. Therefore, breast MRI interpretation by radiologists remains essential. Residents or radiologists with less experience seem to benefit from a CAD system when performing breast MRI evaluation.

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Chapter 5

Quantitative multivoxel proton chemical shift imaging of the breast

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Magn Reson Imaging 2010; 28(3):314-319

Abstract

The study of focal pathology by single voxel magnetic resonance spectroscopy (MRS) is hampered by the impossibility to study tissue heterogeneity or compare the metabolite signals in breast lesion directly to those in unaffected tissue. Multivoxel MRS studies while potentially allowing for truly quantitative tissue characterization, have up to now also been far from quantitative with, for example, the signal-to-noise ratio of the choline (Cho) signal serving as measure of tumor activity. Shown in this study is that in a standard clinical setting with a regular 1.5T magnetic resonance scanner, it is possible to perform quantitative multivoxel MR spectroscopy. With the use of literature values for the T1 and T2 relaxation times of Cho and water in fibroglandular breast tissue and tumors one can determine the concentrations of Cho in different tumor compartments and surrounding tissues in two brief multivoxel MRS measurements. This opens excellent perspectives to quantitative diagnostic and follow-up studies of focal pathology such as lesions suspected of breast cancer.

Introduction

Proton magnetic resonance spectroscopy (MRS) studies of the human breast published to date have been either single voxel [1-16] or multivoxel investigations [15,17-20]. With some exceptions [3,7,16], the metabolites detected by single voxel MRS were documented in, at best, a semi-quantitative fashion such as assessment of the signal-to noise ratio in the choline (Cho) peak, peak visibility, or non-referenced arbitrary peak area units. Furthermore, the study of focal pathology by single voxel MRS will always be hampered by the impossibility to study tissue heterogeneity or compare the metabolite signals in a breast lesion directly to those in unaffected tissue. Multivoxel MRS studies while potentially allowing for truly quantitative tissue characterization, have up to now also been far from quantitative with the use of the Cho signal-to-noise ratio as measure of tumor activity [15,17-20]. This is a rather arbitrary and irreproducible parameter affected by multiple factors such as the B_0 and B_1 field distributions and patient movement. The purpose of this study is to present a quantitative multivoxel MRS method for the examination and metabolic mapping of pathology in the human breast.

Materials and Methods

Magnetic resonance imaging (MRI) and proton (^{1}H) MRS were performed at 1.5T using a Magnetom Avanto system with a body RF coil for excitation and a commercially available circularly polarized breast array receiver coil equipped with automatic tuning and electronic decoupling (Siemens, Erlangen, Germany). The MRI protocol included transverse and sagittal T2 weighted fast spin-echo series covering both breasts (TR/TE 4500/102), performed without distortion correction to optimise MRS planning. After acquisition of the MRS series, T1-weighted MRI (FLASH 2D, 10º pulse angle, TR/TE 4.2/1.3) was performed in the transverse direction and repeated after Gd-contrast agent (0.2 mmol/kg, Dotarem; Guerbet, Villepinte, France) administration.

The multivoxel MRS technique used was an institutional modification of two-dimensional chemical shift imaging (CSI) point-resolved spectroscopy (PRESS) double spin-echo [21,22] with phase-encoding gradients between the slice selective 90° pulse and the first slice-selective

optimized 180° pulse [23]. Two-dimensional CSI of the breast was performed twice, first without suppression of the water and fat signals to serve as a reference measurement and subsequently with suppression of the water and fat signals to be able to detect Cho. The field of view was 8x8 cm to roughly cover the transverse cross section of the examined breast, subdivided into 144 phase encode steps to yield voxels of 0.67x0.67x1 cm at the used slice thickness of 1 cm. In this hybrid CSI technique the volume of interest was smaller than the field of view (3x3x1 cm) in order to end up with essentially measuring the watery part of the breast (glandular breast tissue, pathology). Unwanted water and lipid signals were suppressed by band selective inversion with gradient dephasing [24,25]. This was realized by implementing a frequency selective 180° RF pulse surrounded by two crusher gradient pulses of opposite signs, with PRESS excitation to suppress both water and lipid signals using a minimum phase bandstop pulse designed to pass Cho to N-acetylaspartate resonances and suppress water and lipid signals [25]. Six additional nine-lobe sinc outer volume suppression pulses were applied before excitation, resulting in 6 outer volume suppression slabs of at least 3 cm thickness each on all sides of the volume of interest. Further reduction of the water signal was achieved by chemical shift-selective presaturation [26] and by water reference post-processing (next paragraph). 512 data points were acquired at a band width of 1250 Hz resulting in a data acquisition time of 410 ms. In the first measurement without suppression of any signal the repetition time (TR) and echo time (TE) were set at 1500 ms and 30 ms, respectively [27]. The TE was kept small in order to minimize loss of water and fat peak intensities due to T2 relaxation and the TR was set at 1500 ms in order to limit the acquisition time to 4:46 min. The second measurement was performed at the same TR and at a longer TE (135 ms) in order to be able to presaturate the water signal and to reduce the impact of residual fat signals on the spectral baseline (acquisition time 4:46 min).

In the postprocessing the 12x12 phase encode steps were interpolated into a 16x16 matrix, i.e. voxels appearing as 0.5x0.5x1 cm^3. The number of peaks fitted included the chemical shift ranges restricted to 3.15-3.3 ppm for the $N(CH_3)_3$ group of Cho, 2.9-3.1 for the NCH_3 group of creatine (Cr), 4.5-5.0 ppm for water, and 1.0-1.5 ppm for the main resonance of fat ($-CH_2-$). Using standardized postprocessing protocols, the raw data were processed automatically, allowing for operator-idependent quantifications. The postprocessing protocol for the water and fat suppressed series consisted of water reference processing, hanning filtering (width

700 ms, center 0 ms), zero filling from 512 to 1024 data points, Fourier transformation, polynomial baseline correction (with the above peak ranges excluded), phase correction and curve fitting to Gaussian line shapes using the standard scanner software.

The concentrations of the metabolites Cho and Cr were calculated from the relative peak areas of the resonances of Cho ($N(CH_3)_3$ at 3.23 ppm) or Cr (NCH_3 at 3.01 ppm), denoted S_M, and water (H_2O at 4.7 ppm) using the following formula:

$$[M] = S_M/S_{H2O} \times TWC \times 1/Mw_{H2O} \times n_{H2O}/n_M \times T1sat_{H2O}/T1sat_M \times T2sat_{H2O}/T2sat_M \quad (1)$$

In order to report concentrations in a molar (moles per liter of tissue volume) unit, literature values were adapted for the tissue water contents (TWC) of voxels containing breast tumor tissue, 82% [28] and fibroglandular breast tissue, 65.3% [29]; n_{H2O} is 2, n_{Cr} is 3 and n_{Cho} is 9. Mw_{H2O} stands for the molecule weight of water. [For simplicity and in order to reduce reliance on literature values, one might want to leave out the TWC correction and report metabolite concentrations per liter of water. One then obtains tumor and fibroglandular tissue metabolite levels that are (1/0.82*100%=) 22% higher and (1/0.653*100%=) 53% higher than the values reported here].

Any difference in receiver gain or scaling factor between the subsequent MRS measurements was corrected for. Furthermore, the processing of all MRS data was repeated without water reference processing to make certain that no lipid artifacts were introduced near the frequencies of Cho end Cr.

The T1-saturation factors and T2-saturation factors for water, Cr and Cho were calculated using the following formulas:

$$T1sat = 1 - \exp(-TR/T1) \quad (2)$$

$$T2sat = \exp(-TE/T2) \quad (3)$$

For the T1 of water in fibroglandular breast tissue we used the means of the values published by Graham et al. [29] (1301 ms) and Rakow-Penner at al. [30] (1333 ms), i.e. 1317 ms. For the T1 of water and Cho in breast tumor we adapted the value of 746 ms and

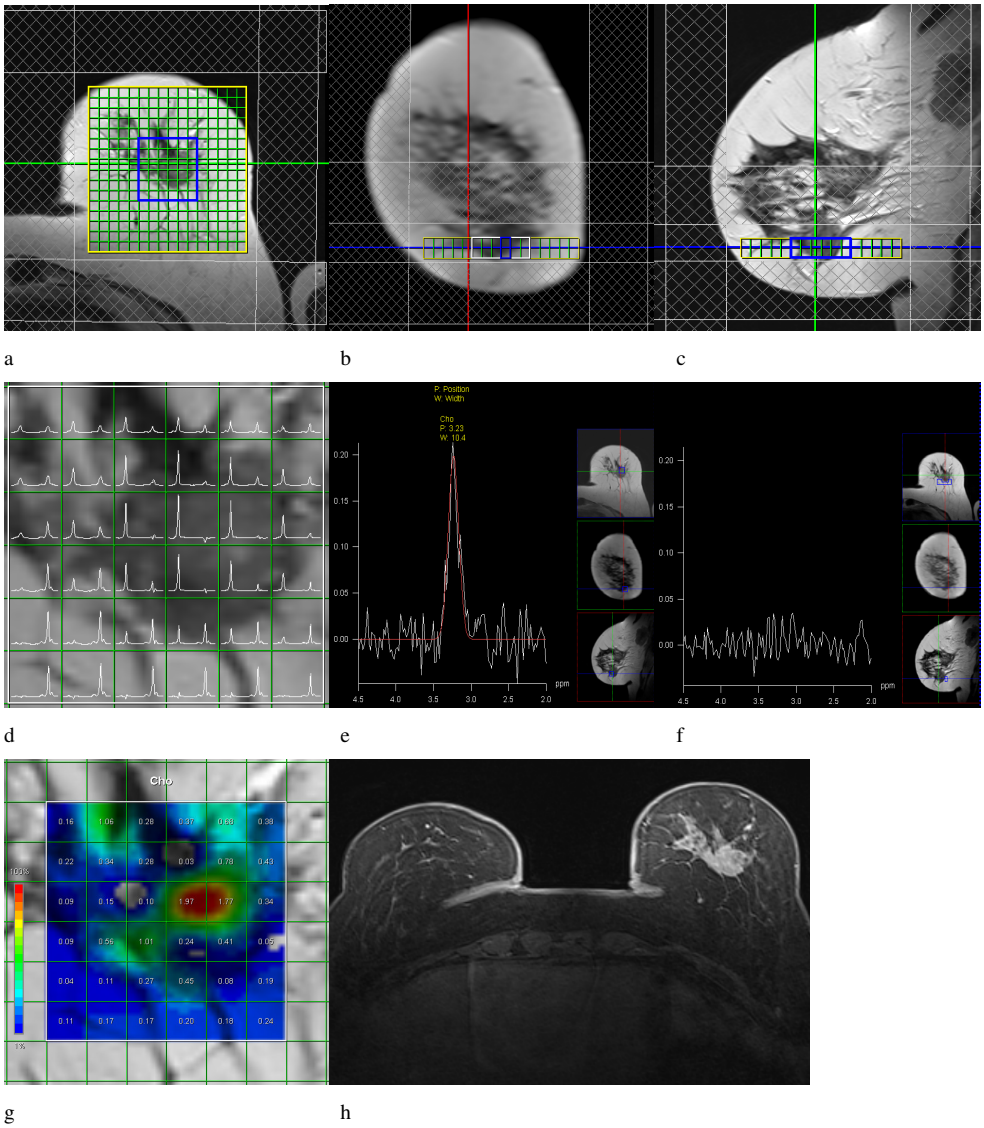
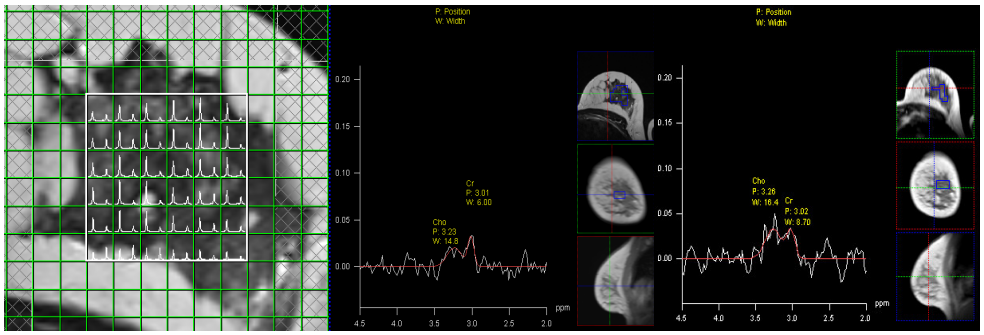


Fig. 1 Volume of interest (36 voxels of 0.25 cm^3 each) centered on an adenocarcinoma in the left breast of a 53 year old patient (a-c) and a spectral map showing intense water and minor fat peaks in the lesion (d). After application of water and fat suppression, an intense Cho peak is detected in tumor (e) as compared with no signal in adipose tissue (f). The tumor shows up as hyperintense in the Cho map (g). After administration of Gd-contrast, tumor and surrounding areas are hyperintense on T1-weighted MRI (h).

1513 ms, respectively, published by Baik et al. [12]. Lacking literature values, we used the T1 of Cho in normal brain tissue (1240 ms) [31] as the value to be expected in fibroglandular tissue. For the T2 of water in fibroglandular tissue we used the means of the values published by Graham et al. [29] (40 ms) and Rakow-Penner at al. [30] (58 ms), i.e.49 ms. For the T2 of water in breast tumor, we adapted the value of 97 ms published by Baik et al. [12]. For the T2 of Cho in breast tumor, we used the means of the values published by Bakken (340 ms) [32] and Baik (269 ms) [12], i.e. 305 ms. Lacking literature values, we used the T2 of Cho in normal brain tissue (311 ms) [31] as the value to be expected in fibroglandular tissue. For the T1 and T2 of the N-CH_3 group of Cr (3.01 ppm), detected in fibroglandular tissue only, the relaxation times published for normal brain tissue (T1 = 1580 ms, T2 = 225 ms) were used [31].

Results

The feasibility of the CSI method is demonstrated in two patients (examined by MRI/MRS with informed consent) whose pathologies were confirmed by biopsy. For a 53 year old patient suffering from an invasive ductal carcinoma of the left breast, figure 1 shows the volume of interest (36 voxels of 0.25 cm^3 each) centered on the tumor (a-c). The spectral



a b c

Fig. 2 Volume of interest (36 voxels of 0.25 cm^3 each) centered on fibroglandular tissue in the left breast of a 32 year old control subject with CSI spectral map showing intense water and minor fat peaks in most voxels (a). After application of water and fat suppression, minor Cho and Cr peaks are detected in the fibroglandular tissue (b). A similar result is obtained in the same subject reexamined by the same method 4 weeks later (c).

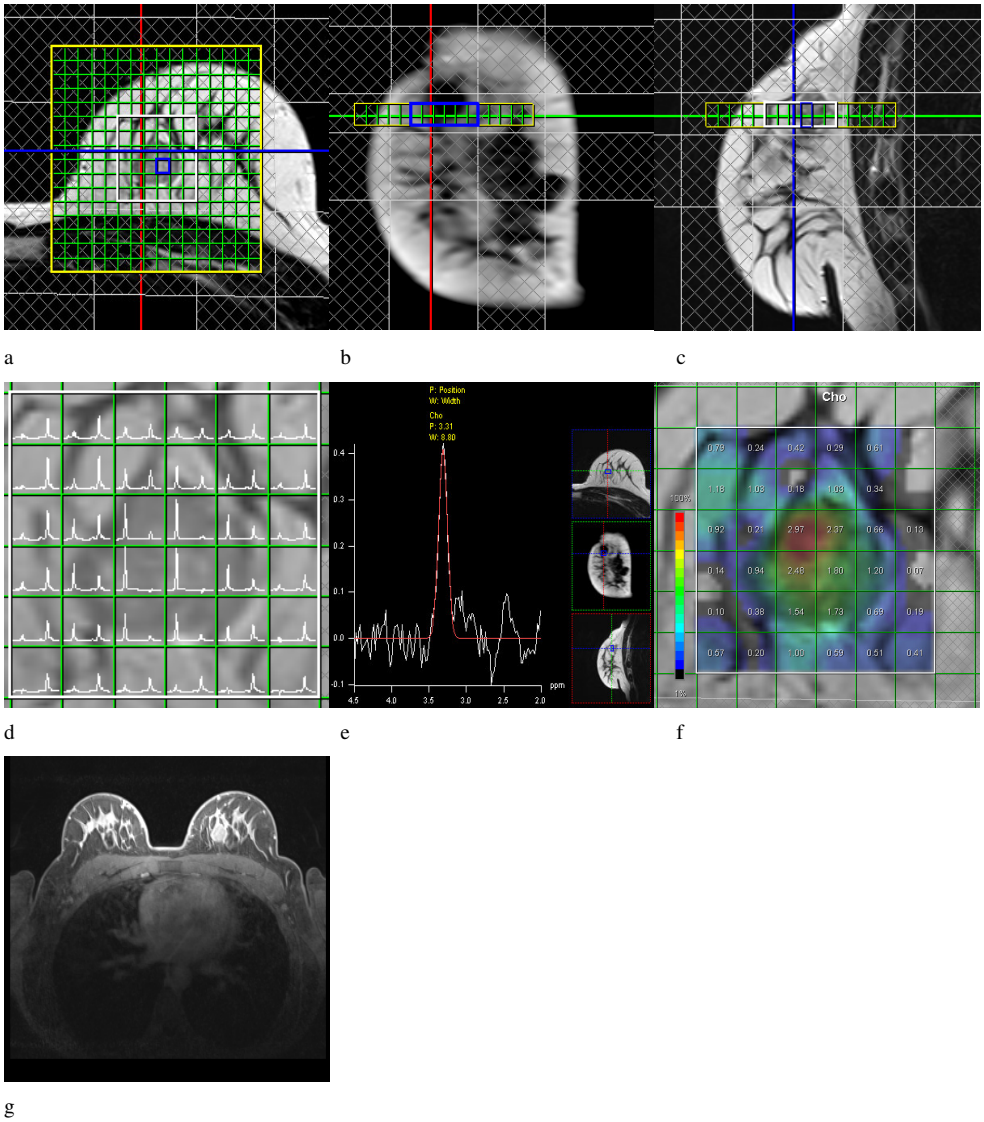


Fig. 3 Volume of interest (36 voxels of 0.25 cm^3 each) centered on an invasive ductal carcinoma in the left breast of a 38 years old patient (a-c) and a spectral map showing intense water and minor fat peaks in the lesion (d). After application of water and fat suppression, an intense Cho peak is detected in tumor (e). The tumor shows up as hyperintense in the Cho map (f). After administration of Gd-contrast, the tumor is amongst those areas that are hyperintense on T1 weighted MRI (g).

map of the first CSI measurement without any suppression of the water and fat signals shows intense water (left side, 4.7 ppm) and minor fat peaks (right side 1.3 ppm) for each voxel containing lesion (Fig.1d). After application of water and fat suppression, in 4 tumor voxels an intense Cho peak is detected at 3.23 ppm (Fig.1e) as compared with no signal in 9 voxels containing adipose tissue (Fig.1f) and the minor Cho and Cr signals in the fibroglandular tissue of a healthy control subject aged 32 years examined twice (Fig.2). The tumor shows up as hyperintense in the metabolic map of Cho (Fig.1g). At 10 minutes afterthe administration of Gd-contrast agent, tumor and surrounding areas are hyperintense on T1 weighted MRI acquired with a water-only excitation pulse (Fig.1h). Figure 3 shows similar results for an invasive ductal carcinoma in a patient of 38 years old.

Using equations 1 to 3 and the relaxation times cited in Materials and Methods, the following concentrations are calculated: In the 4 tumor voxels of the first example (Fig.1e) the mean concentration of Cho is 2.8 mM. The highest level encountered in one of the 4 tumor voxels is 4.1 mM. Mere noise was measured in the adipose tissue from the same volume of interest. In the fibroglandular breast tissue of the healthy younger woman serving as control (Fig.2) Cho and Cr concentrations of 0.3 and 0.8 mM, respectively, are calculated at the first examination (Fig.2b) and of 0.6 and 0.8 mM at another examination performed 4 weeks later (Fig.2c). The mean Cho concentration in the second tumor example is 3.4 mM (means of 8 voxels) and the maximum is 4.6 mM.

Discussion

In this study, we have shown that in a standard clinical setting with use of a regular 1.5T MR scanner, it is possible to perform quantitative multivoxel MRS. With the use of literature values for the T1 and T2 relaxation times of Cho, Cr and water in fibroglandular breast tissue and tumors, one can determine the concentrations of metabolites in different tumor compartments and surrounding tissues in two brief multivoxel MRS measurements. As is always the case in quantitative MRS, one has to rely on multiple assumptions. However, the great advantage of converting metabolite peak areas into concentrations (mM) is that true comparisons can be made, between different patients and pathologic entities as well as in the monitoring of tumor metabolism while the patient is treated for

breast cancer. This opens excellent perspectives to quantitative diagnostic and follow-up studies of focal pathology such as lesions suspected of breast cancer.

Breast tumor levels of Cho, widely accepted as prime tumor marker in proton MRS [33] near 2 mM have been observed by single voxel MRS using the water signal as internal reference [7,16]. Considering, also, that in brain metastases of breast cancer Cho concentrations of up to 4 mM have been observed [34], the tumor Cho concentration of up to 4.1 mM observed here, exceeding that in fibroglandular tissue by one order of magnitude, appears in agreement. Noted here is that in normal brain, the level of Cho also is rather high, 1.72 mM in white matter tissue and 1.54 mM in gray matter tissue [35]. It should be noted that these two patients were the first ones with confirmed breast cancer examined at our institution. Different levels may be detected in subsequent patients. We have thus shown that multivoxel CSI is able to detect tumor Cho at low concentrations. In our CSI method, as in any quantitative MRS approach of tumor characterization, a limitation is the use of literature T1 and T2 values for determining the saturation factors affecting quantification. It is obvious that T1 and T2 varies between tumor types and patients and may even change significantly during therapy [36]. Our healthy volunteer data, yielding fibroglandular Cho contents of 0.3 and 0.6 mM in the same person reexamined 4 weeks apart, indicate that the reproducibility of breast CSI measured Cho content is in the order of 0.3 mM.

We believe that the current widespread practice of single voxel or non-quantitative multivoxel MRS examination of breast cancer is inadequate. Quantitative multivoxel MRS can now be performed in less than 10 minutes, even when using a daily routine 1.5T MRI system, and should therefore be used for the examination and metabolic mapping of pathology in the human breast.

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Chapter 6

Determination of choline concentration in breast lesions: Quantitative multivoxel proton MR spectroscopy as a promising noninvasive assessment tool to exclude benign lesions

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Abstract

Purpose: To determine the optimal cutoff of choline (Cho) concentration in quantitative multivoxel magnetic resonance (MR) spectroscopic data to safely prove benignancy in breast lesions.

Materials and Methods: The study was institutional review board approved, and informed consent was obtained from each patient. Between July 2009 and July 2010, multivoxel MR spectroscopy was performed in 24 consecutive patients with 25 breast lesions assessed as Breast Imaging Reporting and Data System 3 or 4 and larger than 1 cm in diameter at mammography. Two-dimensional point-resolved spatially localized spectroscopy chemical shift imaging was first performed without signal suppression (repetition time msec/echo time msec, 1500/30) as reference measurement and was performed subsequently with suppression of water and fat signals (1500/135) to detect Cho. Differences in mean and highest Cho concentration in the breast lesions were tested for significance by using the independent sample *t* test. The final diagnosis was confirmed with pathologic findings.

Results: Fourteen of 25 breast lesions were malignant. The mean Cho concentration varied between 0.3 and 1.3 mmol/L (0.84 mmol/L ± 0.32 [standard deviation]) in benign lesions and between 1.3 and 9.5 mmol/L (3.10 mmol/L ± 2.21) in malignant lesions. The highest Cho concentrations in benign and malignant lesions were 0.4–1.5 mmol/L (1.19 mmol/L ± 0.33) and 1.7–11.8 mmol/L (4.08 mmol/L ± 2.81), respectively. Mean and highest Cho concentrations in benign and malignant breast lesions differed significantly (P = .02 for both).

Conclusions: The study, in a relatively small patient population, shows that quantitative multivoxel MR spectroscopy can be applied to exclude benign breast lesions from further invasive diagnostic work-up with the implementation of a Cho concentration of 1.5 mmol/L or lower as a cutoff. Further larger studies will be needed to confirm these results.

Introduction

In vivo proton magnetic resonance (MR) spectroscopy is a noninvasive technique that can provide tumor metabolic information. MR spectroscopy has been increasingly applied for the evaluation of breast lesions and therapy response monitoring [1-28]. The diagnostic value of MR spectroscopy is generally based on the detection of elevated levels of choline-containing compounds (Cho), which are markers of an active malignant breast tumor.

MR spectroscopy can be performed as single- [1-21] or multivoxel [22-28] technique. The single-voxel technique has limitations in terms of lesion coverage, which may affect the sensitivity of the assessment of Cho from just one voxel in view of tumor heterogeneity [22,26]. Multivoxel MR spectroscopy, referred to as spectroscopic imaging or chemical shift imaging, acquires spectroscopic information from a large volume of interest subdivided into an array of voxels measured in a single measurement [22-28]. Therefore, the multivoxel MR spectroscopic technique is suitable for analyzing the regional distribution of tumor metabolites and studying tissue heterogeneity. Another advantage of multivoxel MR spectroscopy is the possibility of metabolic mapping of breast lesions [26].

Several single-voxel MR spectroscopic studies conducted at 1.5T have shown the results of the single-voxel technique for differentiating between malignant and benign breast lesions on the of the detection of Cho (peak visibility or Cho signal-to-noise ratio) [1-21]. However, in studies Cho signals were also detected in benign lesions and normal breast tissues [3-5,11,13]. Therefore, the presence of a Cho-related peak in breast MR spectroscopy is not sufficient for a noninvasive diagnosis of malignancy. Quantification of the peak of Cho is required to determine the accurate levels of Cho.

Although, with the possibility of mapping Cho distributions, the multivoxel MR spectroscopic technique is potentially suited for performing truly quantitative tissue characterization, previous multivoxel MR spectroscopic studies have up to now been far from quantitative, with the use of the Cho signal-to-noise ratio as measure of tumor activity [22,24,25,28]. One recent study [26] presented a quantitative multivoxel MR spectroscopic method for the examination and metabolic mapping of disease in the human breast. With the use of literature values for T1 and T2 relaxation times of Cho and water in fibroglandular breast tissue and tumors, the concentration of Cho can be determined in

different tumor compartments and surrounding tissues in two brief multivoxel MR spectroscopic measurements [26]. The purpose of this study is to determine the optimal cutoff of Cho concentration in quantitative multivoxel MR spectroscopic data to exclude benign lesions from further invasive diagnostic work-up.

Materials and Methods

Patient population

This prospective study was conducted between July 2009 and July 2010 at the University Medical Center Groningen. Twenty-four consecutive patients (mean age, 48.4 years; age range, 32–69 years) with 25 breast lesions (irrespective whether the lesion was palpable or not) assessed as Breast Imaging Reporting and Data System (BI-RADS) 3 or 4 and larger than 1 cm in diameter at mammography underwent multivoxel MR spectroscopy. Patients were excluded if there was a history of breast cancer, hematoma of the breast, or previous breast surgery including breast implants. Referral indication for mammography was recorded. The final diagnosis of the breast lesions was confirmed by using histologic or cytologic findings of the breast lesion. Tissue samples were obtained by using ultrasonographically (US) guided fine-needle aspiration biopsy (n = 3), US-guided core biopsy (n = 21), or MR-guided vacuum-assisted core biopsy (n = 1). This study was approved by the Medical Ethical Committee of the University Medical Center Groningen. Informed consent was obtained from each patient prior to the study. The clinicians and patients were not informed of the results from MR spectroscopy.

MR imaging and MR spectroscopy

MR imaging was performed at 1.5 T by using a whole-body MR imager (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) with a body radiofrequency coil for excitation and a commercially available circularly polarized bilateral breast phased-array receiver coil with automatic tuning and electronic decoupling (Siemens Medical Solutions), with the patient in the prone position. The MR imaging protocol included diffusion-weighted imaging with b values of 0, 50, 200, 500, 800, and 1000 sec/mm^2 and transverse T2-weighted turbo spin-echo imaging (repetition time msec/echo time msec,

4500/102; field of view, 340 mm; section thickness, 4 mm). A transverse and sagittal T2-weighted fast spin-echo series covering both breasts (4500/102) was performed without distortion correction for MR spectroscopy planning. For the spectroscopic imaging technique, the MR spectroscopic protocol of Sijens et al. [26] was used. This protocol included two-dimensional chemical shift imaging with double-spin-echo point-resolved spatially localized spectroscopy with phase-encoding gradients between the section-selective 90° pulse and the first section-selective optimized 180° pulse. Two-dimensional chemical shift imaging of the breast was performed twice, first without suppression of water and fat signals (1500/30) to serve as a reference measurement. The echo time was kept small to minimize loss of water and fat peak intensities due to T2 relaxation, and the repetition time was set at 1500 msec to limit the acquisition time to 4 minutes 46 seconds. The second measurement was with suppression of water and fat signals (1500/135) to be able to detect Cho. The same repetition time and a longer echo time (135 msec) were used to be able to presaturate the water signal and to reduce the effect of residual fat signals on the spectral baseline (acquisition time, 4 minutes 46 seconds). The total MR spectroscopic acquisition time therefore was less than 10 minutes.

The field of view was 8 × 8 cm to roughly cover the transverse cross section of the examined breast and was subdivided into 144 phase-encode steps at the used section thickness of 1 cm. In this hybrid chemical shift imaging technique, the volume of interest, on which the automated adjustments of B_0 field (shimming), frequency, transmitter gain, and receiver attenuation were performed, was smaller than the field of view (3 × 3 × 1 cm) to end up with essentially measuring the watery part of the breast (glandular breast tissue and/or disease). The bandwidth was 1300 Hz (corresponding with a section-select gradient of approximately 1 mT/m), which caused a chemical shift displacement error of 1.5 mm between the metabolic maps of Cho and water. In our data analysis, this small effect was not corrected for. Unwanted water and lipid signals were suppressed with band-selective inversion with gradient dephasing [26].

No intravenous contrast material at MR imaging was administered to the patients prior to the MR spectroscopy to prevent possible interference of metal chelate with the detectability of Cho [29,30]. Contrast material was administered afterward, but, in this study, the results of dynamic contrast material–enhanced MR imaging were not assessed, which prohibited

us from evaluating the incremental benefit of the incorporation of MR spectroscopy into the MR imaging diagnostics of breast cancer.

Data analysis

The MR spectroscopic measurements were performed in breast lesions larger than 1 cm in diameter at mammography that were localized on diffusion- and T2-weighted images; the results of MR spectroscopy then were projected on the transverse T2-weighted MR imaging series. A standard software package (Syngo; Siemens) was used for postprocessing MR spectroscopic data. The 12 × 12 phase-encode steps were interpolated into a 16 × 16 matrix (ie, voxels appearing as 0.5 × 0.5 × 1 cm). The number of peaks fitted included the chemical shift ranges restricted to 2.9–3.1 ppm for creatine, 3.1–3.4 ppm for Cho, 4.5–5.0 ppm for water, and 1.0–1.5 ppm for the main resonance of fat ($-CH_2-$). By using standardized postprocessing protocols, the raw data were processed automatically, allowing for operator-independent quantifications. To further minimize the amount of arbitrary operator input, no use was made of the possibility of retrospective voxel shifting.

The concentration of the metabolite Cho was calculated from the relative peak areas of the resonances of Cho ($N(CH_3)_3$ at 3.23 ppm), denoted S_M, and water (H_2O at 4.7 ppm) by using the following equation:

$$[Cho] = S_M/S_{H2O} \times TWC \times 1/Mw_{H2O} \times n_{H2O}/n_M \times T1sat_{H2O}/T1sat_M \times T2sat_{H2O}/T2sat_M$$

where *S* is signal, M is metabolic Cho, TWC is tissue water content, Mw is molecular weight, *n* is number of hydrogen nuclei, and sat is saturation. To make the method robust, concentrations were reported in a molar unit (ie, in moles per liter of voxel volume regardless of the composition, such as tumor, extracellular fluids, glandular tissue). For this purpose, the water signal (peak area) in the lesion voxels is considered to be equal to 91 mol/L, that is, the literature value for the tissue water content of voxels containing breast tumor tissue, or 82% [28] of the molar proton content of pure water ($2 \cdot 1000/18 = 111$ mol/L); n_{H2O} is 2 and n_M is 9. The T1 and T2 saturation factors for water and Cho were calculated by using literature values for T1 and T2 relaxation times of water and Cho as described by Sijens et al [26].

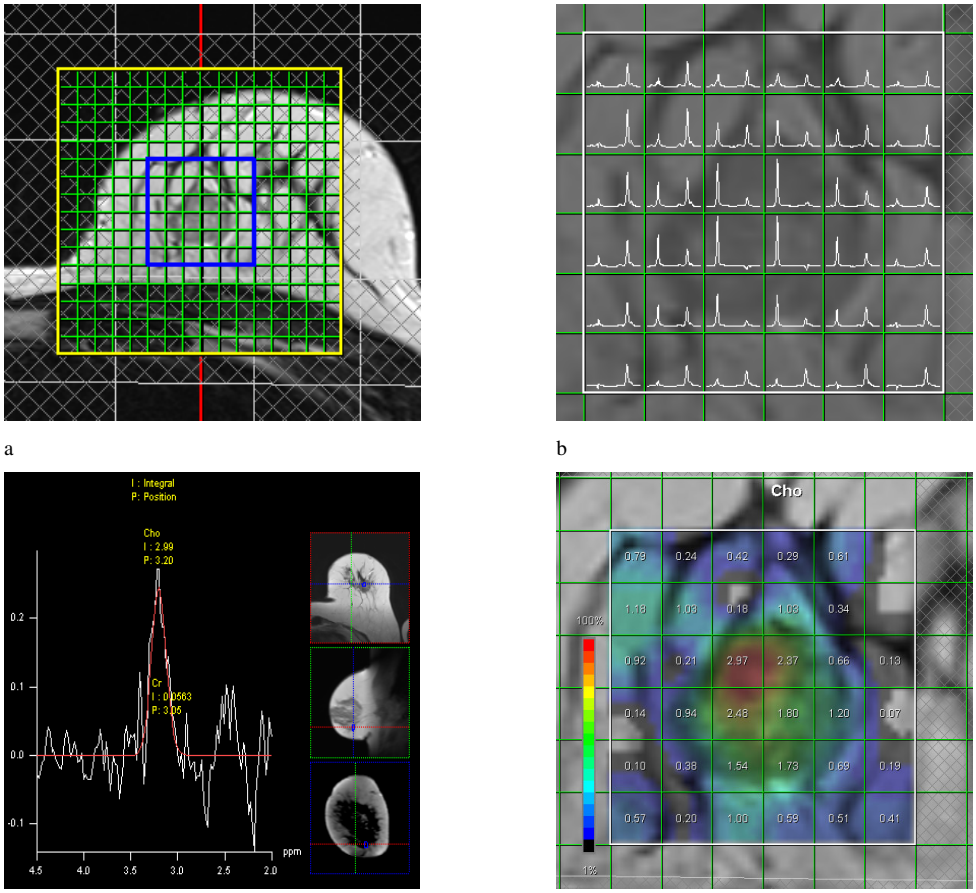
Lesion voxels were defined as voxels matching the lesion location at MR imaging and having a water signal larger than the fat signal. The above procedure of deriving lesion Cho concentrations from the unsuppressed water signal thus led to values corrected for partial volume effect of adipose tissue (characterized by intense lipid signals and very little water, resulting in decreasing water reference signal in proportion to the adipose fraction). Note that the metabolic maps of Cho, as shown in the figures, are not corrected for partial volume effect, which means that these reflect the distribution of Cho signals over the entire volume of interest regardless of the spatial distributions of water and fat, rather than the water-fraction Cho concentrations as could be calculated by using the respective water fractions on a voxel-by-voxel basis.

Statistical analysis

The mean and standard deviation of the Cho peak, the mean Cho concentration, and the highest Cho concentration of all benign and malignant lesions were calculated. Differences between benign and malignant breast lesions concerning the Cho measurements were tested for significance by using the independent sample *t* test. A *P* value less than .05 was considered to indicate a statistically significant difference. Data were analyzed with software (SPSS, version 16.0, 2009; SPSS, Chicago, Ill).

Results

The indication for undergoing mammographic examination was a palpable breast lesion in 16 (67%) patients. In three (13%) patients, a suspicious (nonpalpable) lesion was found at screening mammography performed by the Dutch National Breast Cancer Screening Program. Three (13%) patients were screened outside the National Screening Program because they were at high risk for breast cancer at young age, and two (8%) patients had an enlarged lymph node in the axilla without any breast symptoms.



a b

c d

Fig. 1 Transverse MR image shows volume of interest (36 voxels of 0.25 cm^3 each) centered on an invasive ductal carcinoma in the left breast of 38-year-old woman (a).Spectral map shows intense water and minor fat peaks in the lesion (b). After application of water and fat suppression, an intens Cho peak is detected in the tumor , as shown on spectra. MR images are inset (c). Cho map shows intense Cho peak as hyperintense (d). *Cr* = creatine

Breast lesions

Twenty-five breast lesions exceeding 1 cm on the mammogram were assessed. (One patient had a mammographic BI-RADS 3 lesion and a BI-RADS 4 lesion in the left breast.) Ten (40%) of 25 breast lesions were classified as BI-RADS 3, and 15 (60%) were classified as BI-RADS 4 on the mammogram. One (10%) of 10 mammographic BI-RADS 3 lesions was malignant, and 13 (87%) of 15 BI-RADS 4 lesions were malignant (Table 1). The size of

the benign lesions as seen at MR imaging varied between 10 and 21 mm. For malignant lesions, the size was between 10 and 58 mm.

Table 1 Mammographic BI-RADS classification and disease in 25 breast lesions.

BI-RADS Classification and Disease	Size on MR image (mm)	Biopsy method
BI-RADS 3 (n=10)		
Fibroadenoma (n=4)	13, 12, 10, 10	US-guided core biopsy
No malignant cells (n=3)	12.5, 14, 10	Fine-needle aspiration biopsy
Fibrosis with apocrine metaplasie (n=1)	13	MR-guided vacuum-assisted core biopsy
Lobular hyperplasia without atypia (n=1)	19	US-guided core biopsy
Invasive ductal carcinoma (n=1)	10	US-guided core biopsy
BI-RADS 4 (n=15)		
Invasive ductal carcinoma (n=10)	33, 29, 24, 17, 27 34, 15, 16, 21, 41	US-guided core biopsy
Invasive lobular carcinoma (n=2)	15, 20	US-guided core biopsy
Metaplastic carcinoma (n=1)	11	US-guided core biopsy
Fibroadenoma (n=1)	15	US-guided core biopsy
Epithelial hyperplasia without atypia (n=1)	10	US-guided core biopsy

Multivoxel MR spectroscopy

The volume of interest (36 voxels of 0.25 cm^3 each after postprocessing) was centered on the breast lesion (Fig. 1, 2). For malignant lesions, after application of water and fat suppression, Cho peak was intense in voxels containing malignant tumor and was negligible outside the lesion (Fig. 1c, 1d). For benign lesions, the Cho peak was not nearly as prominent as in malignant tumors, although, as seen on the metabolic map, still exceeds the levels of Cho in voxels outside the lesion (Fig. 2c, 2d).

The number of voxels used for calculating the mean and the highest Cho concentration in 25 breast lesions varied from 2 to 7 voxels, with an average of 4 voxels. The Cho peak of 14 malignant and 11 benign breast lesions was detected in the spectrum between 3.08 and 3.23 ppm (3.18 ppm ± 0.05 [standard deviation]) and 3.14 and 3.34 ppm (3.24 ppm ± 0.07) (P = .04), respectively (Tables 2, 3).

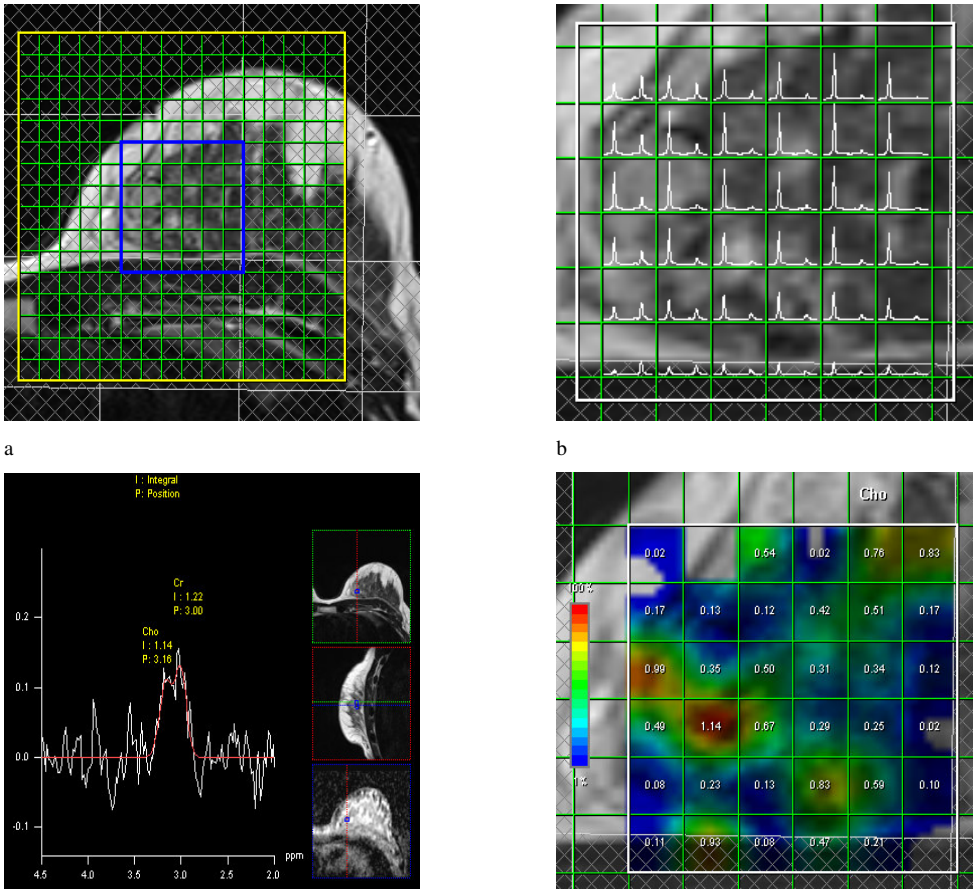


Fig. 2 Transverse MR image shows volume of interest (36 voxels of 0.25 cm^3 each) centered on a benign fibroadenoma in the left breast of 44-year- old woman (a).Spectral map shows intense water and minor fat peaks in most of the volume of interest (b). After application of water and fat suppression, a small Cho peak is detected (also some creatine *[Cr]*) in the lesion, as shown on spectra. MR images are inset (c). Cho map shows small Cho peak as hyperintense (d).

For the 14 malignant breast lesions, the mean Cho concentration varied between 1.3 and 9.5 mmol/L (3.10 mmol/L ± 2.21), and the highest Cho concentration varied between 1.7 and 11.8 mmol/L (4.08 mmol/L ± 2.81). For the 11 invasive ductal carcinomas, the highest Cho concentration ranged from 1.7 to 6.8 mmol/L, and for two invasive lobular carcinomas, it ranged from 2.3 to 11.8 mmol/L. The metaplastic carcinoma had a highest Cho concentration of 3.9 mmol/L (Table 2).

The mean Cho concentration of the 11 benign breast lesions was between 0.3 and 1.3 mmol/L (0.84 mmol/L ± 0.32), and the highest Cho concentration was between 0.4 and 1.5 mmol/L (1.19 mmol/L ± 0.33). For the five fibroadenomas, the highest Cho concentration ranged from 0.4 to 1.3 mmol/L. For the three breast lesions that showed no malignant cells after fine-needle aspiration biopsy, the highest Cho concentration varied between 0.8 and 1.5 mmol/L. The lobular hyperplasia and epithelial hyperplasia lesions had a highest Cho concentration of 1.0 and 1.4 mmol/L, respectively. Fibrosis with apocrine metaplasia showed a highest Cho concentration of 1.5 mmol/L (Table 2).

Table 2 Number of voxels, Cho peak, and mean and highest Cho concentration for 14 malignant and 11 benign breast lesions.

Disease	No. of Voxels	Cho peak (ppm)	Mean Cho conc (mmol/l)	Highest Cho conc (mmol/l)
Malignant lesions (n=14)				
Invasive ductal carcinoma (n=11)	2	3.14	1.6	1.7
	2	3.23	1.3	1.8
	2	3.20	1.6	1.8
	3	3.14	2.1	2.2
	4	3.23	1.4	2.4
	3	3.14	1.7	2.5
	4	3.23	2.8	4.1
	4	3.20	4.1	4.4
	6	3.20	3.4	4.6
	7	3.18	4.7	6.8
	4	3.23	4.9	6.8
Invasive lobular carcinoma (n=2)	2	3.14	2.0	2.3
	5	3.08	9.5	11.8
Metaplastic carcinoma (n=1)	7	3.18	2.4	3.9
Benign lesions (n=11)				
Fibroadenoma (n=5)	6	3.32	0.3	0.4
	6	3.17	0.9	1.3
	2	3.16	1.0	1.3
	2	3.22	1.1	1.3
	2	3.17	1.3	1.3
No malignant cells (n=3)	4	3.31	0.4	0.8
	2	3.27	0.9	1.3
	4	3.34	0.8	1.5
Fibrosis with apocrine metaplasie (n=1)	4	3.30	0.6	1.5
Lobular hyperplasia without atypia (n=1)	4	3.20	0.7	1.0
Epithelial hyperplasia without atypia (n=1)	5	3.14	1.2	1.4

There was a similar significant difference between benign and malignant lesions for the mean and the highest Cho concentration (P = .02 for both) (Table 3). Furthermore, with regard to the highest Cho concentration, there was no overlap between the values for benign (0.4–1.5 mmol/L) and malignant (1.7–11.8 mmol/L) lesions. With regard to the mean benign and malignant Cho concentration, the ranges overlapped at 1.3 mmol/L (0.3–1.3 vs 1.3–9.5 mmol/L, respectively).

Table 3 The mean and the standard deviation for Cho peak and mean and highest Cho concentration in benign and malignant lesions.

Measurement	Benign lesions (n=11)	Malignant lesions (n=14)	*P*-value
Cho peak (ppm)	3.24 ± 0.07	3.18 ± 0.05	.04
Mean Cho concentration (mmol/L)	0.84 ± 0.32	3.10 ± 2.21	.02
Highest Cho concentration (mmol/L)	1.19 ± 0.33	4.08 ± 2.81	.02

Discussion

MR spectroscopy is a noninvasive technique that has not yet fulfilled its potential of being able to help reliably differentiate between benign and malignant breast lesions. Most of the studies published to date used single-voxel MR spectroscopic method [1-21]. The remainder are multivoxel studies, preferable in oncology, because those studies are able to provide improved metabolic assessment, given the inherent tissue heterogeneity, owing to improved sampling approaches with high spectral resolution and large spatial coverage. Qualitative or semiquantitative multivoxel measurements were previously used for the detection of Cho (i.e. detectibility or Cho signal-to-noise ratio) [22-25,27,28]. In our study, a recently published multivoxel MR spectroscopic method based on quantitative measurement was implemented [26]. We provided a strong indication that the lesion Cho concentration in millimolars as a cutoff, namely 1.5 mmol/L, can be applied to exclude benign breast lesions, such as fibroadenomas, from further invasive diagnostic work-up.

However, with respect to the small sample size, larger studies are needed to verify these results.

A limitation was the larger than 1 cm lesion size that we required for study inclusion. With MRI systems of 3.0T or higher, the expected gain in signal-to-noise ratio should enable implementation of our MR spectroscopic method at higher spatial resolution (smaller voxels enabling the detection of smaller tumors).

There have been single-voxel MR spectroscopic studies proposing quantification of Cho peak by using an external reference method with known concentrations or an internal reference method [2,5,13,21]. With the use of an external reference method, there is no correction for partial volume of adipose tissue in the voxel [21]. Alternatively, using water as an internal reference automatically compensates for partial volume effect and does not require separate calibration experiments [2,5]. A limitation was the assumption that water content does not change during varying pathological conditions [2,5]. Moreover, the variation of water content may be quite large, depending on the placement of the voxel, but internal referencing may correct for this. Whereas these single-voxel studies [2,5,13,21] have demonstrated their use for quantification of Cho concentrations in breast lesions, single-voxel MR spectroscopic technique will always be hampered by a lack of direct comparison of the metabolite signals in breast lesions with those in unaffected tissue. Furthermore, there is a loss of sensitivity of the assessment of Cho from just one single voxel in view of tumor heterogeneity [22,26].

The high spectral resolution and large spatial coverage of multivoxel technique make it advantageous over the single-voxel technique. The external and internal reference methods that had been used in single-voxel techniques are not practical for the multivoxel technique because of the requirement of a long imaging time to measure correction factors (eg, receiver gain, partial volume effects, and T1 and T2 relaxation times, etc.). Furthermore, a good reference acquisition and good water and fat suppression are needed for quantification, which may not be achieved given the field inhomogeneity across the large chemical shift imaging grid [22]. In our study, the latter problem was overcome by measuring a volume of interest considerably smaller than the entire chemical shift imaging grid (3x3x1 cm of 8x8x1 cm). Nevertheless, the method applied here also has technical limitations related to partial volume averaging effects, water and fat suppression, spatial

under-sampling, whole breast coverage in acceptable imaging times and quantification. At the modest volume of interest used in this study, B_0 inhomogeneity and B_1 inhomogeneity did not present problems, but with large chemical shift imaging volumes, the effectivity of water and fat suppression may be compromised. The wings or sidebands of the much larger residual water and lipids signals could lead to ambiguous detection of the Cho signal because of the overlap. We acknowledge that for 8 of 25 lesions with only 2 out of 36 voxels (Table 2) the chemical shift imaging approach cannot be substantially different from a single-voxel approach. The fact remains that in our quantitative multivoxel MR spectroscopic study, improved methods for water and fat suppression [26] have enhanced the detectability of Cho and thus facilitated the measurements of its mean and highest concentration in both benign and malignant lesions.

In previous chemical shift imaging studies of breast tumors [22,24,25], the peak intensity of Cho was measured in the lesion and expressed relative to the background noise level (signal-to-noise ratio), which is a far from quantitative measurement of Cho because signal-to-noise ratio depends on multiple unpredictable factors that vary among examinations. In the study of Beak et al. [22] which yielded the highest accuracy, at the optimal cutoff of Cho, signal-to-noise ratio greater than 3.2, the number of false-negative cases was five [22]. The present study indicates that with the highest Cho concentration of 1.5 mmol/L or lower as a cutoff, rather than a signal-to-noise ratio, no malignant lesions were falsely scored as benign. Nevertheless, our quantitative approach also has drawbacks, including assumptions as to the water content of the lesion and its relaxation times, factors affecting the precision, and accuracy of the Cho concentrations.

In our study, a significant difference between benign and malignant lesions is found both in the mean (P = .02) and the highest (P = .02) Cho concentration. However, this statistical analysis was based on comparisons between groups of lesions. For the diagnosis of an individual patient, the highest Cho concentration is advised rather than the mean Cho concentration, because in the former data set there was no overlap between the outcome of benign and malignant lesions at 0.4–1.5 mmol/L versus 1.7–11.8 mmol/L, respectively. Another argument for the highest Cho concentration method is that, especially in large tumors covered by multiple MR spectroscopic voxels, the maximum Cho level encountered in a cross section is a more objective measure than the lesion average. The latter is

determined by the arbitrary setting of the borders of the lesion and decisions as to whether to include necrotic and cystic areas.

Furthermore, there is a tendency of chemical shifts of Cho in malignant and benign breast lesions to be different (P = .04). Stanwell et al. [14] and Stanwell and Mountford [27] suggested that the spectrum obtained in a malignant breast lesion has a resonance at 3.23 ppm, interpreted as representative of phosphocholine, whereas the spectrum obtained in fibroadenoma has a resonance at frequency of 3.28 ppm because of differences in the biochemical contents of the nonmalignant tissue (eg, in the individual or combined levels of glycerophosphocholine, taurine, or myoinositol) [14,27]. However, in our data, overlap between the position of Cho peak in the spectrum for malignant and benign lesions was large, 3.08-3.23 ppm versus 3.14-3.34 ppm, respectively. This indicates that there is no specific frequency of the Cho peak in the spectrum related to malignancy.

A limitation in our present study was that we did not assess the results of dynamic contrast-enhanced MR imaging, which prohibited us from evaluating the incremental benefit of the incorporation of MR spectroscopy into the MR imaging diagnostics of breast cancer.

In conclusion, the finding in this feasibility study that breast lesions with a volume of 1 cm^3 or greater and a Cho concentration of 1.5 mmol/L or lower are benign indicates that, in this patient group, multivoxel MR spectroscopy can potentially replace invasive diagnostic work-up. However, further research is needed to verify the cutoff of 1.5 mmol/L in a prospective analysis with a larger sample size.

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Chapter 7

The added value of quantitative multi-voxel MR spectroscopy in breast Magnetic Resonance Imaging

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Abstract

Purpose: To determine whether quantitative multivoxel MR spectroscopy improves the accuracy of MRI in the assessment of breast lesions.

Materials and Methods: Twenty-five consecutive patients with 26 breast lesions ≥1 cm assessed as BI-RADS 3 or 4 with mammography underwent quantitative multivoxel MR spectroscopy and contrast-enhanced MRI. The MR spectroscopic technique used was 2D-CSI with PRESS to measure the choline (Cho) concentration as calculated from the unsuppressed water signal. ROC analysis was used to quantify the diagnostic accuracy of MRI and MR spectroscopy in the assessment of breast lesions.

Results: Mean Cho concentrations in 26 breast lesions classified by MRI as BI-RADS 2 (n=5), 3 (n=8), 4 (n=5) and 5 (n=8) were 1.16±0.43SD, 1.43±0.47SD, 2.98±2.15SD and 4.94±3.10SD mM, respectively. Two of the BI-RADS 3 lesions and all BI-RADS 4 and 5 lesions were malignant on pathology and had Cho concentrations between 1.7-11.8mM (4.03±2.72SD), which was significantly higher (P = .01) than the Cho in the 11 benign lesions (all BI-RADS 2 lesions and 6 out of 8 BI-RADS 3 lesions) of 0.4-1.5mM (1.19±0.33SD). Furthermore, Cho concentrations between the benign and malignant breast lesions in BI-RADS 3 category differed (P = .01). The accuracy of multivoxel MR spectroscopy added to the breast MRI BI-RADS classification (AUC = 1.00) exceeded the accuracy of MRI alone (AUC = 0.96±0.03).

Conclusions: These preliminary data indicate that multivoxel MR spectroscopy improves the accuracy of MRI in the assessment of breast lesions, especially in BI-RADS 3 category. If further research confirms that breast lesions with a volume ≥1cm^3 and Cho concentrations up to 1.5mM are benign, this could prevent invasive procedures in the diagnostic work-up.

Introduction

Breast Magnetic Resonance Imaging (MRI) is emerging as an important diagnostic modality. With the use of morphological characteristics and kinetic analysis of breast lesions on MRI, the sensitivity of breast MRI approaches 90% whereas the overall specificity of breast MRI varies between 67% and 72% [1-3]**.** Although the negative predictive value (NPV) of MRI in breast cancer is the highest of all imaging techniques (97%) [4-6], meaning that in most cases a negative breast MRI can safely rule out malignancy**,** breast MRI alone is still not the perfect modality.

The fourth edition of the Breast Imaging Reporting and Data System (BI-RADS) Atlas includes a new lexicon for breast MRI that promotes the standardization of lesion descriptors and assessment categories [7]. This lexicon is based on the results of International Working Group on Breast MRI and the American College of Radiology (ACR) Breast MRI Lexicon Committee and includes a BI-RADS 3 assessment category [7-10]. The suggested work-up of these probably benign findings is a short-time interval follow-up or biopsy. At this moment most approaches are intuitive [11,12]. It can be expected that the majority of patients thus referred for biopsy have a benign lesion.

In addition to morphologic and kinetic analysis, metabolic information is considered useful for the assessment of breast lesions. A promising approach to clarify the precise nature (benign or malignant) of a lesion is the use of a non-invasive MRI method which is referred to as MR spectroscopy [13,14]. The diagnostic value of MR spectroscopy is typically based on the detection of elevated levels of choline (Cho) compounds. MR spectroscopic studies of the breast have been either single-voxel [13-33] or multivoxel [34-40] investigations. The single-voxel technique has limitations in terms of lesion coverage. The general practice of including either the entire lesion or just its center in the voxel, may result in dilution of the elevated Cho levels in vital malignant tumor by contributing necrotic and cystic tumor areas with low Cho levels, resulting in false negatives [34,38].

The multivoxel MR spectroscopic technique or chemical-shift imaging (CSI) acquires spectroscopic information from a large volume of interest subdivided into an array of voxels measured in a single measurement and has potential for performing truly quantitative tissue characterization [34-40]. This is necessary because Cho signals are not

only detected in malignant breast lesion but also in benign breast lesions and normal fibroglandular tissue [13,14,17,23,25,36]. Recently, multivoxel MR spectroscopy was used for measurement of the Cho concentrations encountered in breast lesions [38].

The purpose of this study is to determine whether the Cho level measured by quantitative multivoxel MR spectroscopy can increase the accuracy of contrast-enhanced MRI in the assessment of breast lesions.

Materials and Methods

Patient population

This prospective study was conducted between July 2009 and July 2010 at the University Medical Center Groningen and was approved by the Medical Ethical Committee of the University of Groningen. Informed consent was obtained form each patient prior to the study.

Twenty-five consecutive patients (mean age: 48.7 years, age range: 32-69) with 26 breast lesions ≥ 1cm assessed as BI-RADS 3 or BI-RADS 4 with mammography underwent multivoxel MR spectroscopy and contrast-enhanced MRI. Patients were excluded if there was a history of breast cancer, a hematoma of the breast or previous breast surgery including breast implants. The final diagnosis of the breast lesions was based on cytology or histology, considered as the gold standard. Tissue samples were obtained by ultrasound-guided fine needle aspiration biopsy (FNAB) (n=3), ultrasound-guided core biopsy (n=5), MR-guided vacuum-assisted core biopsy (n=1) or surgery (n=17).

MR imaging

MR scans were performed at 1.5T using a whole body MRI system (Avanto; Siemens Medical Solutions, Erlangen, Germany) with a dedicated bilateral breast coil and the patient in prone position. The standard MRI protocol included diffusion weighted imaging (DWI) with b-values 0, 50, 200, 500, 800 and 1000. A T2 turbo spin echo (Repetition Time (TR)/ Echo Time (TE) 4500/102ms, FOV 340mm and slice thickness 4mm) was performed in the transversal plane. A T1 weighted three-dimensional (3D) DynaVIEWS sequence (TR/TE/FA 4.17ms/1.29ms/10deg, FOV 340mm and slice thickness 0.97mm, totally

1.04min) in the transversal plane was made before and 7 times after intravenous administration of 0.1 mmol/kg DOTAREM (0.5mmol Gd/ml). The total duration of the dynamic study was approximately 9 minutes.

Multivoxel MR spectroscopy

The breast lesion was localized on DWI and T2 weighted images. After the location of the breast lesion was determined the transverse and sagittal T2-weighted fast spin-echo series covering both breasts (TR/TE 4500/102ms) performed without distortion correction were used for MR spectroscopy planning. The spectroscopic imaging protocol [38] included 2D-CSI with point resolved spectroscopy (PRESS) double spin-echo with phase-encoding gradients between the slice selective 90^0 pulse and the first slice-selective optimized 180^0 pulse. 2D-CSI of the breast was performed twice, first without suppression of the water and fat signals (TR/TE 1500/30ms) to serve as a reference measurement. The second measurement was with suppression of the water and fat signals (TR/TE 1500/135ms) (acquisition time 4:46 min). The field of view was 8x8 cm to roughly cover the transverse cross section of the examined breast, subdivided into 144 phase encode steps to yield voxels of 0.67x0.67x1 cm at the used slice thickness of 1 cm. In this hybrid CSI technique the volume of interest was smaller than the field of view (3x3x1 cm) in order to end up with essentially measuring the watery part of the breast (glandular breast tissue, pathology). Unwanted water and lipid signals were suppressed by band selective inversion with gradient dephasing (BASING) [38].

The multivoxel MR spectroscopy was performed before the T1-weighted images with contrast administration to prevent possible interference of metal chelate with the detectability of Cho [41,42].

Data analysis

MR imaging

Subtracted images were obtained by subtracting pre-contrast images from the post-contrast images using commercially available software. MRI scans were coded using the ordered categories of the ACR BI-RADS lexicon [7]**.** The MR images were classified as normal if

no enhancement was seen in the expected location of the mammographic finding (BI-RADS 1) or only homogeneous or stippled enhancement was found in the breast, representing normal enhancing breast parenchyma or fibrocystic changes (BI-RADS 2). The lesions which were detected on the MRI and corresponded with the area to the mammographic finding were classified as focus, mass enhancement or non-mass enhancement. From the enhancing lesions the location, lesion type, shape, border, distribution, internal enhancement and kinetic curves according to the BI-RADS lexicon were assessed and the lesions were classified as BI-RADS 3, 4 or 5 [7].

Multivoxel MR spectroscopy

In the post-processing 12x12 phase encode steps were interpolated into a 16x16 matrix, i.e. voxels appearing as 0.5x0.5x1 cm^3. The number of MR spectroscopic peaks fitted included the chemical shift ranges restricted to 3.1-3.3 ppm for Cho, 4.5-5.0 ppm for water, and 1.0-1.5 ppm for the main resonance of fat ($-CH_2-$). Standardized postprocessing protocols were used for processing the raw data automatically, allowing for operator-independent quantifications.

For each lesion the highest concentration of the metabolite Cho amongst the various corresponding voxels was calculated from the relative peak areas of the resonances of Cho ($N(CH_3)_3$ at 3.23 ppm), denoted S_M, and water (H_2O at 4.7 ppm) using the following formula:

$$[S_M] = S_M/S_{H2O} \times TWC \times 1/Mw_{H2O} \times n_{H2O}/n_M \times T1sat_{H2O}/T1sat_M \times T2sat_{H2O}/T2sat_M$$

To express concentrations in molar units (mol/L of tissue volume), literature values were adapted for the tissue water contents (TWC) of voxels containing breast tumour tissue, 82% [28]: n_{H2O} is 2, and n_{Cho} is 9. Mw_{H2O} stands for the molecule weight of water.

The T1 saturation factors and T2 saturation factors for water, Cr and Cho were calculated using literature values for T1 and T2 relaxation times of water and Cho as described elsewhere [38].

Statistical analysis

Breast lesions which MRI classified as BI-RADS 2 were considered benign and BI-RADS 3, 4 and 5 lesions were considered positive for malignancy. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of breast contrast-enhanced MRI were calculated on the basis of final pathology reports.

The mean and standard deviation of the highest Cho concentration of, respectively, all benign and malignant lesions were calculated. Differences between the Cho measurements of benign and malignant breast lesions were tested for significance using the independent sample T test. A *P*-value < .05 was considered as statistically significant. Receiver operating characteristics (ROC) analysis was used to quantify the diagnostic accuracy of contrast-enhanced MRI and multivoxel MR spectroscopy in the assessment of breast lesions. Data were analyzed in SPSS 16.0 (SPSS inc 2009, Chicago) and STATA SE version 11.0 (STATA, College Station, Tex.).

Results

The indication for undergoing mammographic examination was a palpable breast lesion in 17 (68.0%) patients. In 3 (12.0%) patients a suspicious lesion was found during the National Dutch Breast Cancer Screenings Programme. Three (12.0%) patients were screened because of high risk for breast cancer. Two (8.0%) patients had a mammography because of an enlarged lymph node in the axilla.

Breast lesions

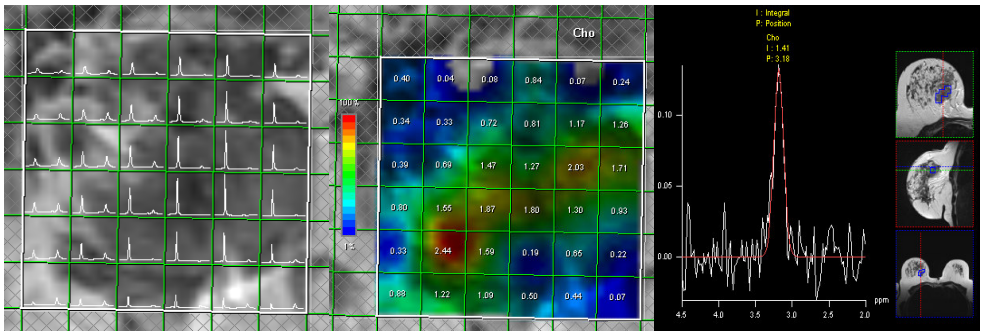
Twenty-six breast lesions were assessed (1 patient had both a mammographic BI-RADS 3 lesion and a BI-RADS 4 lesion in the same breast). Ten (38.5%) out of 26 breast lesions were classified as BI-RADS 3 and 16 (61.5%) breast lesions as BI-RADS 4 on the mammogram. The size of the benign lesions as seen on MRI varied between 10 and 21 mm. For malignant lesions the size was 10 to 80 mm.

Table 1 MRI BI-RADS classification, number of voxels and the mean and standard deviation (SD) of the highest Cho concentration in benign and malignant breast lesions.

MRI BI-RADS Classification (number of benign+malignant lesions)	Number of voxels (range)	Highest Cho concentration (mM) (mean±SD)			
		Total	Benign	Malignant	*P*-value
5 BI-RADS 2 lesions (5+0)	2-6	1.16±0.43	1.16±0.43		
8 BI-RADS 3 lesions (6+2)	2-6	1.43±0.47	1.22±0.26	2.05±0.35	.01
5 BI-RADS 4 lesions (0+5)	2-7	2.98±2.15		2.98±2.15	
8 BI-RADS 5 lesions (0+8)	3-14	4.94±3.10		4.94±3.10	
Total			1.19±0.33	4.03±2.72	.01

MRI BI-RADS classification and multivoxel MR spectroscopy

MRI classified the 26 breast lesions as BI-RADS 2 (n=5; 19.2%), as BI-RADS 3 (n=8; 30.8%), as BI-RADS 4 (n=5; 19.2%) and as BI-RADS 5 (n=8; 30.8%). The means of the highest Cho concentrations detected in these BI-RADS categories were 1.16±0.43SD for five BI-RADS 2 lesions, 1.43±0.47SD for eight BI-RADS 3 lesions, 2.98±2.15SD for five BI-RADS 4 lesions and 4.94±3.10SD for eight BI-RADS 5 lesions (Table 1).



a b c

Fig. 1 Volume of interest (36 voxels of 0.25 cm^3 each) centered on an invasive lobular carcinoma in the right breast of a 67-year- old patient and spectral map showing intense water and minor fat peaks in the lesion (a). After application of water and fat suppression intense Cho signals are detected in the whole lesion as shown in green on the metabolic map (b). The highest detected Cho level (the red voxel in the metabolic map) is used for quantification. The sum of all tumor MR spectra together is shown in (c).

The five BI-RADS 2 lesions with a mean Cho concentration of 1.16mM were benign: 3 fibroadenomas and 2 showed no malignant cells after FNAB.

Two out of eight BI-RADS 3 lesions turned out to be malignant and showed a mean Cho concentration of 2.05mM. These 2 breast lesions were an invasive ductal carcinoma and an invasive lobulair carcinoma. The other six MRI BI-RADS 3 lesions were benign and had a mean Cho concentration of 1.22mM. One out of 6 benign breast lesions showed no malignant cells in the FNAB and the histology of the other five lesions were: 2 fibroadenomas, lobular hyperplasia without atypia, epithelial hyperplasia without atypia and fibrosis with apocrine metaplasia. There was a significant difference in Cho concentration between the benign and malignant breast lesions in BI-RADS 3 category (*P*=.01).

All five MRI BI-RADS 4 lesions and all eight MRI BI-RADS 5 lesions with a mean Cho concentration of 2.98mM and 4.94mM, respectively, showed malignancy after surgery: 10 invasive ductal carcinomas, 2 invasive lobular carcinoma (Fig. 1) and 1 metaplastic carcinoma.

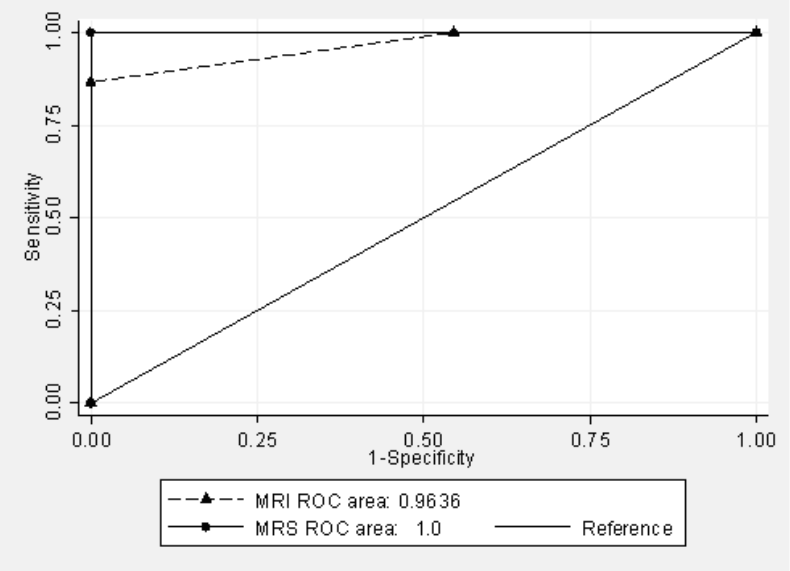


Fig. 2 ROC curves for the comparison of breast MRI and multivoxel MR spectroscopy in the assessment of breast lesions.

There was a significant difference between all benign and malignant lesions for the Cho concentration (P = .01). Furthermore, there was no overlap between the ranges in benign (0.4-1.5mM (1.19±0.33SD)) and malignant lesions (1.7-11.8mM (4.03±2.72SD)) (Table 1, 2).

Breast MRI without multivoxel MR spectroscopy had a sensitivity of 100%, specificity of 45.5%, PPV of 71.4% and NPV of 100%. ROC analysis revealed an area under the curve (AUC) of 0.96±0.03 (95% CI: 0.91-1.00) for the accuracy of breast MRI in the assessment of breast lesions. Using a threshold of the Cho concentration of 1.5mM as the distinction between benign en malignant lesions, the ROC analysis for multivoxel MR spectroscopy revealed an AUC of 1.00 (95% CI: 1.00-1.00) (Fig. 2).

Table 2 Mammographic and MRI BI-RADS classification, number of voxels, the highest Cho concentration and pathology for 26 breast lesions.

Mammographic BI-RADS categroy	MRI BI-RADS category	No. of voxels	Highest Cho conc (mmol/l)	Pathology
10 BI-RADS 3	4 BI-RADS 2	6	0.4	Fibroadenoma
		2	1.3	Fibroadenoma
		2	1.3	No malignant cells
		4	1.5	No malignant cells
	5 BI-RADS 3	6	1.3	Fibroadenoma
		2	1.3	Fibroadenoma
		4	1.5	Fibrosis with apocrine metaplasie
		4	1.0	Lobular hyperplasia without atypia
		4	0.8	No malignant cells
	1 BI-RADS 4	4	2.4	Invasive ductal carcinoma
16 BI-RADS 4	1 BI-RADS 2	2	1.3	Fibroadenoma
	3 BI-RADS 3	5	1.4	Epithelial hyperplasia without atypia
		2	1.8	Invasive ductal carcinoma
		2	2.3	Invasive lobular carcinoma
	4 BI-RADS 4	2	1.7	Invasive ductal carcinoma
		2	1.8	Invasive ductal carcinoma
		3	2.2	Invasive ductal carcinoma
		7	6.8	Invasive ductal carcinoma
	8 BI-RADS 5	3	2.5	Invasive ductal carcinoma
		4	4.1	Invasive ductal carcinoma
		4	2.4	Invasive ductal carcinoma
		6	4.6	Invasive ductal carcinoma
		4	6.8	Invasive ductal carcinoma
		5	11.8	Invasive lobular carcinoma
		14	3.4	Invasive lobular carcinoma (Fig. 1)
		7	3.9	Metaplastic carcinoma

Discussion

Breast MRI is an important diagnostic modality and with a NPV of 97% [4-6] it can safely exclude malignancy. Also in this study the NPV of breast MRI is very high (100%) and therefore no further invasive diagnostic work-up is needed when breast lesions are assessed as BI-RADS 2 with MRI. However, breast MRI is still not perfect. Today BI-RADS is the communication tool in breast MRI reports and the most difficult breast lesions are the lesions which are classified as BI-RADS 3 with MRI. The probability of a mammographic BI-RADS 3 lesion being cancer is considered to be less than 2 % by AHQR [11], but the acceptable cancer yield is not clearly defined for MRI BI-RADS 3 lesions. There are 5 articles that included data in the MRI BI-RADS 3 assessment category, with a resulting wide range of cancer yields (0.6-10%) [4,43-46]. Although, the diagnostic work-up of a BI-RADS 3 lesion can be a biopsy (instead of a follow-up breast MRI after six months) over 90% of patients who are referred for biopsy have a benign disease.

This present study indicates that non-invasive quantitative multivoxel MR spectroscopic technique can be an additional tool for contrast-enhanced MRI in the assessment of breast lesions. The accuracy of breast MRI is excellent, but according to our preliminary results multivoxel MR spectroscopy show an AUC of 1.00. There was no overlap between the outcomes of benign and malignant lesions for the highest Cho concentration, 0.4-1.5 mM and 1.7-11.8 mM, respectively. Cho concentrations over 1.5 mM are not found in benign lesions, such as fibroadenomas. In our study benign breast lesions which were classified as BI-RADS 3 with MRI had a highest Cho concentration $\leq$ 1.5mM and were significantly different (P = .01) from malignant BI-RADS 3 lesions. In this way patients with benign BI-RADS 3 lesion can be excluded from further invasive diagnostic work-up. Accordingly, it can be expected that the added value of noninvasive multivoxel MR spectroscopy applies to the MRI classified BI-RADS 3 lesions.

There are only 3 previous studies featuring the diagnostic value of combined contrast-enhanced MRI and multivoxel MR spectroscopy in evaluating breast lesions. The conclusion of these 3 studies is that multivoxel MR spectroscopy appears to be a promising technique for classification of breast lesions when contrast-enhanced MRI results are equivocal. Since of the clinical practice in the use of contrast-enhanced MRI as diagnostic

tool is to reach a high sensitivity at the cost of the specificity, the metabolic information measured by multivoxel MR spectroscopy may be used to improve the specificity in the diagnosis of breast tumors [34,36,37]. In the study of Beak et al. [34] multivoxel MR spectroscopy had a sensitivity of 81%, specificity of 78% and overall accuracy of 81% with the use of ROC analysis. These outcomes show a lower sensitivity and specificity then the results in our study. A limitation of the 3 studies is that the area of the Cho was measured in the lesion and expressed relative to the background noise level (signal-to-noise ratio), which is no quantitative measurement of Cho [34,36,37]. In our quantitative multivoxel MR spectroscopic study the detectability of abnormalities in Cho level is improved by the measurement of the highest lesion Cho concentration with the ability to analyze the regional distribution of tumor metabolites.

A limitation of our study is that a small patient population is included. Despite this, it is clear that in these breast lesions there is no overlap between the Cho concentration of benign and malignant breast lesions. Another limitation is that only breast lesions $\geq 1cm^3$ were included, reflecting the limited sensitivity of MR spectroscopy (voxels sixes were 0.25 cm^3). Smaller breast lesions will have the problem that the measured lesion Cho levels are reduced by partial volume effects, reducing the changes of being able to demonstrate a malignant Cho profile. In the future the use of more sensitive MRI scanners operating at 3T and up may be expected to allow for the inclusion of smaller lesions. Also, in this study the breast lesions were assessed on DWI and T2-weighted imaging for the MR spectroscopy planning and not on the contrast-enhanced T1-weighted images to avoid the likely influence of contrast medium on the measured Cho concentration. This can be a problem if the breast lesion is not visible with the first two sequences (DWI and T2). Furthermore, the methodology of this study has some technical limitations regarding to partial volume effects, water and fat suppression, whole breast coverage in acceptable scan times and quantification. Nevertheless, in this quantitative multivoxel MR spectroscopic study Cho concentrations are measured more accurately and a significant difference (P=.01) between benign and malignant lesions for the highest Cho concentration is shown.

In conclusion, this study indicates that the noninvasive quantitative multivoxel MR spectroscopic technique can improve the accuracy of contrast-enhanced MRI in the assessment of breast lesions, especially for breast lesions classified as BI-RADS 3. A Cho

concentration over 1.5 mM is not found in benign breast lesions with a volume ≥1cm^3 and therefore these lesions can be excluded from further diagnostic work-up. Nevertheless, larger patient samples are needed to strengthen these conclusions.

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Chapter 8

Summary

Summary

Worldwide incidence of breast cancer is higher than incidence of other malignancies among women. In the Netherlands approximately one out of eight women will develop breast cancer during life. Although the incidence has increased, mortality has decreased during the last two decades and at the moment the risk of dying of breast cancer is 1 of 26. This reduction in mortality is partly due to early detection of malignancies in screening and partly due to more and better adjuvant therapies.

In **chapter 1** of this thesis a general introduction is given concerning mammography, breast Magnetic Resonance Imaging (MRI), Computer Aided Detection (CAD) systems and MR spectroscopy (MRS).

Mammography is the primary imaging modality for the early detection of breast cancer.

Despite advances in mammographic techniques (digital), mammography still has its limitations with regard to both sensitivity (39%-86%) and specificity (88%-94%), which depends on age and breast density. Mammograms and breast Magnetic Resonance Imaging (MRI) are coded using the ordered categories of the Amercian College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon: category 1, negative (normal finding); category 2, benign finding; category 3, probably benign; category 4, suspicious finding; category 5, highly suggestive of malignancy and category 6, pathologically proven breast cancer. The diagnostic work-up of breast lesions depends on the BI-RADS classification of these lesions. The most difficult mammographic lesions are the lesions which are classified as BI-RADS 3 of which it is not possible to decide whether they are malignant or benign. The probability of a BI-RADS 3 lesion to be malignant is considered to be less than 2%. In recent publications, this percentage seems to have been increased up to approximately 15% in the last 5 years. The diagnostic work-up of a BI-RADS 3 lesion can be a biopsy or follow-up mammography after six months. Because of the limited accuracy of both physical examination and mammography, a large majority of patients referred for biopsy has a benign lesion. Breast MRI is emerging as a clinically useful additional diagnostic tool, but there are sparse data available to support the use of breast MRI as problem solving modality in mammographic BI-RADS 3 lesions and, therefore, it has not been implemented in common practice. However, breast MRI has the

highest overall sensitivity, which usually exceeds 90%, of all imaging techniques. In non-calcified lesions a negative breast MRI shows a sufficient high negative predictive value (NPV>98%) to safely exclude malignancy. Thus, in **chapter 2** the usefulness of breast MRI as a problem solving modality in patients with mammographic BI-RADS 3 lesions is investigated in a meta-analysis. Five out of 61 studies met the inclusion criteria. In two out of these 5 studies the role of breast MRI in non-calcified mammographic BI-RADS 3 lesions was investigated. These 2 studies reported a NPV of 100%. In the other 3 studies, mammographic BI-RADS 3 microcalcifications were included. The NPV of MRI was between 76%-97%. Therefore, breast MRI cannot be implemented as a primary diagnostic tool to evaluate mammographic microcalcifications at this time. Although solid data are sparse, the first ones indicate that breast MRI might be useful as problem solving modality to exclude patients with non-calcified mammographic BI-RADS 3 lesions for further diagnostic work-up.

Therefore, in **chapter 3**, 76 patients with a mammographic BI-RADS 3 lesion underwent breast MRI as diagnostic work-up. The purpose of the study was to investigate whether breast MRI can provide a sufficient NPV to safely rule out malignancy and decrease the percentages of invasive diagnostic procedures in mammographic BI-RADS 3 lesions. Lesions classified as BI-RADS 1 or 2 with MRI were considered negative for malignancy. This was the case for 52 (68.4%) out of 76 patients and no malignancies were found during at least 2 years study follow-up. MRI had a sensitivity of 100% (95% CI: 75-100%), specificity of 82.5% (95% CI: 71-91%), positive predictive value of 54.2% (95% CI: 33-74%) and NPV of 100% (95% CI: 93-100%). In conclusion, breast MRI should be used in a diagnostic strategy for the work-up of non-calcified BI-RADS 3 lesions, because the NPV of MRI is high enough (>98%) to rule out malignancy with sufficient confidence. In the majority of patients (68%) no further invasive diagnostic assessment is needed, when the MRI is assessed as BI-RADS 1 or 2.

The postprocessing and interpretation of breast MRI data is time consuming and operator dependent. Computer Aided Detection (CAD) programs for MR imaging of breast lesions have been developed attempting to standardize and facilitate the interpretation of breast MRI.

CAD systems help the radiologist to determine which lesions are benign and which are malignant by automating extraction and interpretation of kinetic curves (the enhancement pattern of lesions). A state of the art CAD system should automatically identify (almost) all non-calcified lesions suspected of malignancy at mammography. This is reflected by a very high sensitivity and NPV for these non-calcified breast lesions. In a systematic review and meta-analysis **(chapter 4)** the additional value of a CAD system in breast MRI is investigated by assessing radiologists' accuracy in discriminating benign from malignant breast lesions with and without CAD implementation. Experienced radiologists reached comparable pooled sensitivity and specificity before and after using CAD (sensitivity: without CAD: 89%; 95% CI: 78-94%, with CAD: 89%; 95%CI: 81-94%) (specificity: without CAD: 86%; 95% CI: 79-91%, with CAD: 82%; 95% CI: 76-87%). For residents the pooled sensitivity increased from 72% (95% CI: 62-81%) without CAD to 89% (95% CI: 80-94%) with CAD, however, not significantly. Concerning specificity, the results were similar (without CAD: 79%; 95% CI: 69-86%, with CAD: 78%; 95% CI: 69-84%). In conclusion, the assessment of MR images with CAD has little influence on the sensitivity and specificity of the performance of radiologists experienced in breast MRI diagnosis. Therefore, breast MRI interpretation by radiologists remains essential. Residents or radiologists with less experience seem to benefit from a CAD system when performing breast MRI evaluation.

Breast MRI seems to have a sufficiently high NPV for non-calcified breast lesions, when the criteria for these lesions, which are partly based on kinetic and morphological analysis, are applied strictly. The remaining breast lesions (approximately 30%) show considerable overlap in enhancement between benign and malignant breast lesions. Therefore, in some cases (mostly BI-RADS 3 lesions), enhancement patterns may be equivocal and additional diagnostic methods may be needed for clarifications. In addition to morphological and kinetical analysis, metabolic information is expected to be promising for the final diagnosis of breast lesions. In vivo proton (^{1}H) MR spectroscopy of the breast provides metabolic information about the investigated tissue in a non-invasive manner. MR spectroscopy can be performed as single-voxel or multivoxel technique. The diagnostic value of MR spectroscopy is generally based on the detection of elevated levels of choline (Cho) containing compounds, which are, to a certain extent, a marker of an active malignant

breast tumor. Namely, in recent studies Cho signals were also detected in benign lesions and normal breast tissues. Therefore, the presence of a Cho-related peak in breast MR spectroscopy is not sufficient for a non-invasive diagnosis of malignancy. Quantification of the Cho compounds peak is required to determine the accurate levels of Cho. Multivoxel MR spectroscopic studies, while potentially allowing for truly quantitative tissue characterization, have up to now also been far from quantitative with the use of the Cho signal-to-noise ratio as measure of tumor activity. Therefore, in **chapter 5** a quantitative multivoxel MR spectroscopy method for the examination of pathology in the human breast is presented. The concentration of Cho can be determined in different tumor compartments and surrounding tissues in two brief multivoxel MR spectroscopic measurements, even when using a daily routine 1.5T MRI system. In **chapter 6** the optimal cutoff of Cho concentration in quantitative multivoxel MR spectroscopic data to exclude benign lesions from further invasive diagnostic work-up is determined. Multivoxel MR spectroscopy was performed in 24 consecutive patients with 25 breast lesions assessed as BI-RADS 3 or 4, and larger than 1 cm diameter at mammography. Mean and highest Cho concentrations in benign and malignant breast lesions differed significantly (P =.02, both). The results of this study, in a relatively small patient population, show that quantitative multivoxel MR spectroscopy can be applied to exclude benign breast lesions with a volume ≥1 cm^3 from further invasive diagnostic work-up with the implementation of a Cho concentration ≤ 1.5 mM as cutoff. Whether the Cho level measured by quantitative multivoxel MR spectroscopy can increase the accuracy of contrast-enhanced MRI in the assessment of breast lesions is investigated in **chapter 7**. Twenty-five consecutive patients with 26 breast lesions ≥1 cm assessed as BI-RADS 3 or 4 with mammography underwent quantitative multivoxel MR spectroscopy and contrast-enhanced breast MRI. The Cho concentration of 15 malignant breast lesions was significantly higher (P = .01) than the Cho concentration in the 11 benign lesions. Furthermore, Cho concentrations between the benign and malignant lesions which were classified as BI-RADS 3 by MRI differed (P = .01). This study indicates that the accuracy of multivoxel MR spectroscopy added to the breast MRI BI-RADS classification (AUC=1.00) exceeded the accuracy of MRI alone (AUC=0.96±0.03).

Conclusion

The focus of this PhD thesis is to prevent unnecessary invasive procedures in breast cancer diagnostic work-up for women with a probably benign (BI-RADS 3) breast lesion. For mammographic non-calcified BI-RADS 3 lesions breast MRI can provide a sufficiently high NPV (>98%) for early diagnostic work-up and thereby safely rule out malignancy in a majority of patients (68%), herewith avoiding unnecessary invasive diagnostic procedures. The use of a state of the art CAD system should automatically identify (almost) all non-calcified lesions suspected of malignancy, but the implementation of a CAD system for these breast MRIs' evaluation has little influence on the accuracy of the performance of an experienced radiologist. However, short time (10 minutes), non-invasive quantitative multivoxel MR spectroscopy on a 1.5T system can increase the accuracy of breast MRI. A Cho concentration >1.5mM is not found in benign breast lesions with a volume $\geq 1 cm^3$ and therefore these lesions can be excluded from further unnecessary invasive diagnostic procedures. Nevertheless, larger patient samples are needed to strengthen this conclusion and to implement this result in regular care.

Chapter 9

Nederlandse Samenvatting

Samenvatting

De wereldwijde incidentie van borstkanker is hoger dan de incidentie van andere vormen van kanker onder vrouwen. In Nederland krijgt ongeveer 1 op de 8 vrouwen borstkanker. Hoewel de incidentie is gestegen, is de mortaliteit de laatste twee decennia afgenomen en op dit moment is het risico op overlijden aan borstkanker 1 op 26. Deze afname in mortaliteit komt gedeeltelijk door het vroegtijdig opsporen van borstkanker door screening en gedeeltelijk door meer en betere aanvullende behandelingen.

In **hoofdstuk 1** van dit proefschrift wordt een algemene introductie gegeven over mammografie, mamma Magnetic Resonance Imaging (MRI), Computer Aided Detection (CAD) systemen en MR spectroscopie (MRS).

Mammografie is de eerste keus voor het vroegtijdig opsporen van borstkanker. Ondanks de voordelen van mammografie (digitaal), heeft mammografie nog steeds beperkingen met betrekking tot de sensitiviteit (39%-86%) en specificiteit (88%-94%), die afhankelijk zijn van de leeftijd van de vrouw en de dichtheid van het borstweefsel. Mammogrammen en mamma MRI's worden gecodeerd aan de hand van de categorieën van de "Amercian College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS)" lexicon: categorie 1, negatief (normale bevindingen); categorie 2, benigne laesie (=goedaardige afwijking); categorie 3, waarschijnlijk benigne; categorie 4, waarschijnlijk maligne (=kwaadaardig); categorie 5, zeer verdacht voor maligniteit; categorie 6, pathologisch bewezen voor borstkanker. De keuze voor diagnostisch onderzoek van mamma-afwijkingen is afhankelijk van welke BI-RADS categorie is gegeven aan de afwijking. Over de afwijkingen die op het mammogram als BI-RADS 3 geclassificeerd zijn is het niet mogelijk een uitspraak te doen in termen van maligniteit of benigniteit. De kans dat een BI-RADS 3 afwijking maligne is, was voorheen kleiner dan 2% en is tot op heden het uitgangspunt. Dit percentage neemt echter de laatste 5 jaar toe tot circa 15%, gelet op de meer recente publicaties. Het vervolg-diagnostisch onderzoek bij BI-RADS 3 afwijkingen bestaat uit een biopsie procedure of een follow-up na 6 maanden. Vanwege het feit dat het klinisch borstonderzoek en mammografie een beperkte diagnostische accuraatheid hebben, blijkt het merendeel van de patiënten, die een biopsie procedure ondergaan, een benigne afwijking te hebben. Mamma MRI is een klinisch bruikbaar aanvullend diagnostisch

onderzoek, maar er is maar een beperkt aantal studies gedaan die het gebruik van een mamma MRI als probleemoplossend diagnostisch onderzoek bij mammografische BI-RADS 3 afwijkingen ondersteunt. Daarom wordt een mamma MRI niet gebruikt in de dagelijkse praktijk. Echter, mamma MRI heeft, in zijn algemeenheid, de hoogste sensitiviteit van alle beeldvormende technieken, die in de meeste studies de 90% overschrijdt. In niet-gecalcificeerde mamma-afwijkingen heeft een negatieve mamma MRI een zeer hoog negatief voorspellende waarde (NVW>98%) waardoor een maligniteit met een zeer hoge betrouwbaarheid kan worden uitgesloten. Vandaar dat in **hoofdstuk 2** het gebruik van een mamma MRI als probleemoplossend diagnostisch onderzoek in patiënten met een BI-RADS 3 afwijking wordt onderzocht in een meta-analyse. Vijf van de 61 studies voldeden aan de inclusiecriteria. In 2 van deze 5 studies werd de rol van MRI in mammografische niet-gecalcificeerde BI-RADS 3 afwijkingen onderzocht. Deze 2 studies rapporteerde een NVW van 100%. In de ander 3 studies werden mammografisch BI-RADS 3 microcalcificaties geïncludeerd. De NVW van de MRI bij deze ongeselecteerde patiëntengroep was tussen de 76%-97%. MRI dient dan ook niet te worden toegepast als primair diagnosticum bij de aanwezigheid van microcalcificaties. Ondanks het feit dat er weinig studies zijn, tonen de eerste goed opgezette studies aan dat mamma MRI bruikbaar kan zijn als probleemoplossend diagnostisch onderzoek bij patiënten met niet-gecalcificeerde BI-RADS 3 afwijkingen. Om dit in de praktijk vast te stellen ondergingen in de studie in **hoofdstuk 3** 76 patiënten met een mammografische BI-RADS 3 afwijking een mamma MRI als diagnostisch onderzoek. Het doel van deze studie is om te onderzoeken of de NVW van mamma MRI zo hoog is dat een maligniteit betrouwbaar kan worden uitgesloten bij klinische implementatie, met als gevolg dat het percentage invasieve diagnostische procedures in mammografische BI-RADS 3 afwijkingen substantieel wordt verminderd. Afwijkingen die geclassificeerd werden als BI-RADS 1 of 2 op de MRI werden beschouwd als negatief voor maligniteit. Dit was het geval voor 52 (68.4%) van de 76 patiënten, waarbij geen maligniteit werd gevonden gedurende tenminste 2 jaar studie follow-up. MRI had een sensitiviteit van 100% (95% CI: 75-100%), specificiteit van 82.5% (95% CI: 71-91%), positief voorspellende waarde (PVW) van 54.2% (95% CI: 33-74%) en NVW van 100% (95% CI: 93-100%). Conclusie is dat mamma MRI gebruikt kan worden als diagnostisch onderzoek voor niet-gecalcificeerde BI-RADS 3 afwijkingen, omdat de

NVW van MRI zo hoog is (>98%) dat maligniteit betrouwbaar kan worden uitgesloten voor de klinische praktijk. In de meerderheid van de patiënten (68%), wanneer de afwijking op de MRI wordt beoordeeld als BI-RADS 1 of 2, is geen verdere invasief diagnostisch onderzoek nodig.

De postprocessing en het beoordelen van een mamma MRI kost tijd en is afhankelijk van de radioloog. Er zijn Computer Aided Dectection (CAD) programma's ontwikkeld voor het standaardiseren en het vergemakkelijken van het beoordelen van MRI beelden met mamma-afwijkingen. Een CAD systeem helpt de radioloog om een mamma MRI te beoordelen door automatische extractie van beelden en de interpretatie van kinetische curven (het aankleuringspatroon van de afwijkingen). Een "state of the art" CAD syteem zal automatisch alle niet-gecalcificeerde afwijkingen verdacht voor maligniteit op mammografie moeten herkennen. Dit vanwege de hoge sensitiviteit en NVW van niet-gecalcificeerde mamma-afwijkingen. In een systematische review en meta-analyse **(hoofdstuk 4)** wordt de aanvullende waarde van een CAD systeem in mamma MRI onderzocht door te beoordelen hoe nauwkeurig de radioloog is in het onderscheiden van benigne en maligne mamma- afwijkingen met en zonder een CAD systeem. Ervaren radiologen hadden een vergelijkbare gepoolde sensitiviteit en specificiteit voor en na het gebruik van een CAD systeem (sensitiviteit: zonder CAD: 89%; 95% CI: 78-94%, met CAD: 89%; 95%CI: 81-94%) (specificiteit: zonder CAD: 86%; 95% CI: 79-91%, met CAD: 82%; 95% CI: 76-87%). Voor arts-assistenten steeg de gepoolde sensitiviteit van 72% (95% CI: 62-81%) zonder CAD naar 89% (95% CI: 80-94%) met CAD, maar dit was niet significant. De resultaten van de specificiteit waren gelijk (zonder CAD: 79%; 95% CI: 69-86%, met CAD: 78%; 95% CI: 69-84%). Geconcludeerd is dat een CAD systeem weinig invloed heeft op de sensitiviteit en specificiteit van de ervaren radioloog in het beoordelen van mamma MRI beelden. Daarom blijft de visuele interpretatie van de radioloog van essentieel belang. Arts-assistenten of onervaren radiologen hebben wel baat bij het gebruik van een CAD systeem bij het evalueren van een mamma MRI.

Bij strikte toepassing van de criteria voor een negatieve afwijking die ten dele ook op grond van kinetische en morfologische gegevens gemaakt wordt, blijkt dat een mamma MRI een zeer hoge NVW heeft voor niet-gecalcificeerde mamma afwijkingen. De overige afwijkingen (circa 30%) toont een grote overlap in aankleuringspatronen tussen benigne en

maligne afwijkingen. Daarom zal er in een aantal gevallen (vooral bij BI-RADS 3 afwijkingen) geen duidelijkheid over de afwijking zijn en is een aanvullend diagnostisch onderzoek nodig. Als aanvulling op de morfologische en kinetische analyse wordt verwacht dat metabole informatie veelbelovend is voor de einddiagnose van een mamma-afwijking. Met in vivo proton (^{1}H) MR spectroscopie van de mamma wordt op een niet-invasieve methode metabole informatie verkregen van het mammaweefsel. MR spectroscopie kan als single-voxel of als multivoxel techniek worden uitgevoerd. De diagnostische waarde van MR spectroscopie is gebaseerd op het detecteren van verhoogde choline bevattende componenten (Cho), die tot op zekere hoogte als een marker van een actieve maligne mamma afwijking kunnen dienen. In recente studies werden namelijk ook Cho signalen gevonden in benigne mamma afwijkingen en gezond klierweefsel. Dit is de reden dat de aanwezigheid van een Cho piek in mamma MR spectroscopie niet toereikend is voor een niet-invasieve diagnose van een maligne afwijking. Kwantificatie van de Cho piek is vereist om nauwkeurig de hoogte van de Cho concentratie te bepalen. Multivoxel MR spectroscopie studies hebben de potentie om Cho in het mammaweefsel te kwantificeren, maar in de tot nu toe gepubliceerde studies wordt op een niet-kwantitatieve manier, namelijk de Cho signaal-ruis verhouding gemeten voor de tumor activiteit. Daarom wordt in **hoofdstuk 5** een kwantitatieve multivoxel MR spectroscopie methode voor het beoordelen van pathologie in de mamma gepresenteerd. De concentratie van Cho kan bepaald worden in verschillende tumor compartimenten en het omliggende weefsel in 2 korte multivoxel MR spectroscopiemetingen, zelfs bij het gebruik van een 1.5T MRI systeem. In **hoofdstuk 6** wordt het optimale afkappunt van Cho concentratie in kwantitatieve multivoxel MR spectroscopiedata bepaald om benigne afwijkingen uit te sluiten voor verder invasief diagnostisch onderzoek. Multivoxel MR spectroscopie werd toegepast bij 24 vrouwen met 25 mamma-afwijkingen $\geq$ 1 cm en geclassificeerd als BI-RADS 3 of 4 op het mammogram. De gemiddelde en hoogste Cho concentraties in benigne en maligne mamma- afwijkingen verschilden significant van elkaar (P = .02). Deze studie, in een kleine studiepopulatie, laat zien dat kwantitatieve multivoxel MR spectroscopie gebruikt kan worden om patiënten met benigne afwijkingen $\geq$ 1cm uit te sluiten van verder diagnostische procedures als de Cho concentratie van deze afwijkingen $\leq$ 1.5mM.

Of de gemeten Cho concentratie van mamma afwijkingen met kwantitatieve multivoxel MR spectroscopie methode de nauwkeurigheid kan verhogen van een mamma MRI beoordeling wordt onderzocht in **hoofdstuk 7**. 25 Patiënten met 26 mamma afwijkingen ≥1 cm en beoordeeld als BI-RADS 3 of 4 op het mammogram ondergingen kwantitatieve multivoxel MR spectroscopie en mamma MRI. De Cho concentratie van 15 maligne mamma-afwijkingen was significant (P = .01) hoger dan de Cho concentratie in 11 benigne afwijkingen. Verder verschilde de Cho concentratie tussen de benigne en maligne afwijkingen die door de MRI geclassificeerd waren als BI-RADS 3 significant (P = .01). Uit deze studie blijkt dat de nauwkeurigheid van multivoxel MR spectroscopie toegevoegd aan de mamma MRI BI-RADS classificatie (AUC=1.00) in vergelijking met de nauwkeurigheid van mamma MRI alleen (AUC=0.96±0.03) overschrijdt.

Conclusie

De essentie van dit proefschrift is vrouwen met een waarschijnlijk benigne afwijking (BI-RADS 3) onnodige invasieve procedures in diagnostisch borstkanker work-up te besparen. Voor niet-gecalcificeerde mammografische BI-RADS 3 afwijkingen blijkt mamma MRI een zo hoge NVW (>98%) te hebben, dat een maligniteit betrouwbaar kan worden uitgesloten in de meerderheid (68%) van de patiënten met deze classificatie. Hierdoor kunnen onnodige invasieve diagnostische onderzoeken worden voorkomen. Gebruik van een "state of the art" CAD systeem dat is ontworpen om automatisch alle niet-gecalcificeerde afwijkingen verdacht voor maligniteit te herkennen, blijkt bij een ervaren radioloog weinig toe te voegen aan zijn visuele beoordeling van deze mamma MRI's. Wel kan een kortdurend (10 minuten), niet-invasief kwantitatief multivoxel MR-spectroscopieonderzoek op een 1.5T MRI-systeem de nauwkeurigheid van mamma MRI verhogen. In benigne mamma-afwijkingen met een volume ≥1cm^3 werden geen choline concentraties >1.5mM gevonden, waardoor deze afwijkingen uitgesloten kunnen worden van verdere onnodige invasieve diagnostisch procedures. Echter, meer onderzoek in een nog grotere patiëntengroep is nodig om uitspraken te kunnen doen over de implementatie van deze techniek in de dagelijkse praktijk.

Chapter 10

Dankwoord

Dankwoord

In 2007 begonnen als arts-onderzoeker verbonden aan de NELSON studie, maar na een jaar erachter gekomen dat mijn passie ligt bij mammaonderzoek. Uit het niks werd een mooi onderzoek opgebouwd met als resultaat dit proefschrift. Dit was niet mogelijk geweest zonder de hulp van velen. Daarom wil ik iedereen bedanken die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift! Een aantal mensen wil ik graag in het bijzonder bedanken.

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Beste Paul, het eerste wat mij opviel was hoe snel jij een goed manuscript in elkaar kon zetten. Van jou kreeg ik dan ook altijd een snelle reactie en goed commentaar op mijn manuscripten. Ik heb daar heel veel van geleerd. Daarnaast kon ik elk moment van dag bij je aankloppen. Maar wat heb ik ook erg genoten van jouw humor. Ik hoop dat wij samen op het gebied van de spectroscopie nog heel veel bereiken.

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Chapter 11

Curriculum Vitae

Curriculum Vitae

Monique Dorrius was born on the 31th of March 1977 in Delfzijl, the Netherlands. She grew up in Delfzijl and attended high school at the Ommelander College in Appingedam. In September 1997 she studied Medical Imaging and Radiotherapeutic Technology at the Hanzehogeschool in Groningen, where she graduated in 2001.

In September 2000 she started her study in Medicine at the VU University Amsterdam. During her study, she worked for four years in the Antoni van Leeuwenhoek hospital as radiotherapeutic technician. Her clinical rotations were done in VU University Amsterdam, Sint Lucas Andreas hospital in Amsterdam, Spaarne hospital in Hoofddorp and University Medical Center Groningen. She graduated as Medical Doctor in June 2006. She also received a certificate Masterclass Medicine for the research project "Preoperative staging of uterine cervical carcinoma with multichannel CT compared with clinical examination under general anaesthesia", which was done at the University Medical Center Groningen.

After her graduation, she worked during 6 months as a resident at the Internal Medicine Department of the Scheperhospital in Emmen. In January 2007, she started at the department of Radiology of the University Medical Center Groningen performing research for the NELSON study (Dutch-Belgian randomized controlled trail for lung cancer screening in high-risk subjects). After a year, she decided to change her research topic to breast cancer research, which resulted in this PhD thesis. She had several poster presentations at various international congresses, including Radiological Society of North America (RNSA 2008, 2009), European Congress of Radiology (ECR 2010) and European Breast Cancer Conference (EBCC 2008, 2010). Furthermore, in 2010 she was invited to lecture at the Dutch Society Medical Imaging and Radiotherapy, MRI Conference and the Oncology Days. She graduated for the course "Basic course in Regulations and Organization of Clinical Trials (BROK)" in 2010.

In May 2011, she started her residency in Radiology at the University Medical Center Groningen.

Chapter 12

List of publications

List of publications

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Stellingen

Behorend bij het proefschrift

New diagnostic developments to prevent unnecessary invasive procedures in breast cancer diagnostic work-up

1. Breast MRI can rule out malignancy with high confidence due to the very high negative predictive value. *(dit proefschrift)*

2. Breast MRI should be used in any diagnostic strategy for the work-up of non-calcified BI-RADS 3 lesions to avoid unnecessary invasive procedures. *(dit proefschrift)*

3. The clinical implication for CAD systems in assessing breast MRI is to provide easier and faster ways of interpreting the patterns of contrast enhancement. *(dit proefschrift)*

4. The diagnostic performance of the experienced radiologist in evaluating breast lesions with breast MRI is not influenced by the use of CAD. *(dit proefschrift)*

5. Unlike multivoxel MR spectroscopy, measurement outcomes of single-voxel MR spectroscopy cannot be related with certainty to the region of interest of the relevant breast tissue. *(dit proefschrift)*

6. In breast MR spectroscopy, choline concentrations as a measurement of cell membrane metabolism have to be quantified to discriminate benign from malignant lesions. *(dit proefschrift)*

7. Quantitative multivoxel MR spectroscopy can be applied to exclude benign breast lesions ≥ 1 cm^3 from further invasive diagnostic work-up. *(dit proefschrift)*

8. The impact of sensitivity of diagnostic tests is generally underestimated as a tool to exclude patients from further diagnostic work-up.

9. De kosteneffectiviteit van een goed inlevingsvermogen in de patiënt is nauwelijks te overschatten.

10. De integrale samenwerking tussen de afdelingen radiologie en chirurgie moet eigenlijk vanzelfsprekend zijn.

11. We can suffer our entire life over a thought that may not be true. *(Byron Katie)*

12. Er is geen betere deadline dan je uitgerekende datum.

Monique Dorrius
8 juni 2011