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The Value of Preoperative MRI in Breast Cancer Treatment

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Abstract
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Breast magnetic resonance imaging (MRI) remains controversial as an image adjunct in preoperative settings in terms of short-term benefits and there are no survival data from randomized studies. This prospective, randomized, multicentre study included 440 patients (age ≤ 56 y) with breast cancer from three large-volume Swedish breast clinics. Patients were randomized to either preoperative staging with breast MRI in addition to conventional assessment (n = 220) or to a no breast MRI group (n = 220). Treatments of all patients were discussed at multidisciplinary team conferences. Breast MRI provided additional information in 38% of the patients, and this caused a change in treatment plan for 18%. A change from suggested breast conservation to mastectomy occurred in 15%. The in-breast reoperation rate was statistically significantly lower in the MRI group: 5% vs 15% in the control group (P< 0.001). Although there was a higher MRI-related conversion rate from breast conservation to mastectomy, the final number of mastectomies did not differ between the two groups. The positive predictive value (PPV) of all incremental MRI findings was 74% (95% confidence interval, CI, 60–84%) in the group of patients with altered treatment plans and 27% (95% CI 14–44%) in the group of patients without such plans. In 20 of the 22 cases of conversions from breast-conserving surgery to mastectomy, the PPV for the decisive incremental MRI finding was 91% (95% CI 69–98%) and the PPV for the remaining decisive incremental findings was 83% (95% CI 68–92%). The empirical area under the curve for the MRI group based on receiver operating characteristic analysis was 0.85 (95% CI 0.78–0.91). In our retrospective study conducted in Vasteras County Hospital Breast Unit, preoperative MRI did not reduce the reoperation rates: 1.2% in 2018 vs 3.1% in 2016, when no-MRI was performed. Additional findings were observed in 10% of MRI examinations and more often in younger patients for whom mastectomy was suggested more often. MRI resulted in no delay of surgery. After 10 years of follow-up, the risk of relapse or death was 46% higher in the control group than in the MRI group and the risk of death was 27% higher, although the differences were not significant statistically. Locoregional, distant and contralateral recurrence outcomes combined were increased in the control group (P = 0.048). These results indicate that breast MRI significantly reduced the breast reoperation rate and important incremental findings in younger patients, without increasing the final number of mastectomies. These results could not be confirmed by our retrospective study in which MRI had no impact on the re-excision rate. Preoperative breast MRI provided incremental findings with a high degree of concordance with histopathology and resulted in slightly but non-significantly improved disease-free or overall survival rates after 10 years of follow-up.

Keywords: preoperative breast MRI, breast cancer, breast-conserving surgery

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This thesis is dedicated to my "POMB" children, Julian and Alicia.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Gonzalez V, Sandelin K, Karlsson A, Åberg W, Löfgren L, Iliescu G, Eriksson S, Arver B. Preoperative MRI of the breast (POMB) influences primary treatment in breast cancer: a prospective, randomized, multicenter study. World J Surg. 2014 Jul;38(7):1685-93. doi: 10.1007/s00268-014-2605-0.

II. Karlsson A*, Gonzalez V*, Jaraj SJ, Bottai M, Eriksson S, Sandelin K, Arver B. The accuracy of incremental pre-operative breast MRI findings - concordance with histopathology in the Swedish randomized multicenter POMB trial. Eur J Radiol. 2019;114:185-191. doi:10.1016/j.ejrad.2019.03.005.

III. Eriksson J, Gonzalez V, Laxander K, Bergkvist L, Eriksson S. Preoperative MRI in women with newly diagnosed breast cancer - Re-excision rates and additional findings. In manus.

IV. Gonzalez V, Arver B, Löfgren L, Bergkvist L, Sandelin K*, Eriksson S*. Impact of preoperative breast MRI on 10-year survival outcome of patients included in the Swedish randomized multicentre POMB trial. Accepted in British Journal of Surgery Open.

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Contents

Abbreviations

3-D	Three dimensional
ALND	Axillary lymph node dissection
AUC	Area under the curve
BCS	Breast-conserving surgery
BCSS	Breast cancer-specific survival
BI-RADS	Breast Imaging Reporting and Data System
BRCA	BReast CAncer gene
CI	Confidence interval
CISH	Chromogenic in situ hybridization
COMICE	Comparative effectiveness of MRI in breast cancer
CL	Contralateral
CT	Computed tomography
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
EUSOMA	European Society of Breast Cancer Specialists
FISH	Fluorescence in situ hybridization
Gy	Gray
HR	Hazard ratio
HRT	Hormone replacement therapy
IDC	Invasive ductal carcinoma
IF	Incremental finding
ILC	Invasive lobular carcinoma
IHC	Immunohistochemical
IPC	Invasive papillary carcinoma
KS	Karolinska University Hospital
LT	Larger tumour
MF	Multifocality
MG	Mammography
MDT	Multidisciplinary team conferences
MONET	MR mammography of nonpalpable breast tumours
MRI	Magnetic resonance imaging
NAC	Neoadjuvant chemotherapy
NPV	Negative predictive value
NST	No special type
NKBC	National Quality Register for Breast Cancer
OR	Odds ratio

OS	Overall survival
PCR	Polymerase chain reaction
POMB	Preoperative MRI of the breast
PPV	Positive predictive value
ROC	Receiver operating characteristic
RT	Radiotherapy
SLNB	Sentinel lymph node biopsy
SPSS	Statistical Package for the Social Sciences
StG	S:t Goran Hospital
T	Tesla
Tis	Carcinoma in situ
TNBC	Triple-negative breast carcinoma
US	Ultrasonography

1 Introduction

Breast cancer management has undergone rapid evolution during the past decade, attributed to the development of several important clinical areas, such as molecular and stem cell research, refinement of oncoplastic surgery, tailored chemotherapy approaches, more precise radio therapy and advances in imaging technology. Understanding all the aspects of breast disease together with adequate imaging is the key to effective patient care and has led to a substantially improved outcome.

1.1 Anatomy of the human breast

Human breasts are paired fibroadipose organs localized on the anterior upper part of the thorax. The nipple, surrounded by the areolar skin, protrudes from the centre of each breast where 15-20 lactiferous ducts open. The blood supply of the breast comes from three sources. The main source – the internal mammary artery-supplies the medial parts of the breast. The branches of the axillary artery, namely the lateral thoracic, superior thoracic, pectoral branch of the thoracoacromial and subscapular supply the superior and lateral parts of the breast. Lateral mammary branches contribute to the supply of the whole organ. The venous drainage begins around the areola and mainly accompanies the arteries (1). The lymphatics drain excess lymphatic fluid from the breast and are of great importance in the spread of carcinomas. There are 20-30 axillary lymphatic nodes and these drain about 75% of the lymphatic fluid of the breast. There are also lymphatic vessels accompanying the internal mammary artery and vein, draining lymph into parasternal nodes on the ipsilateral side and less commonly to nodes on the contralateral side (1, 2).

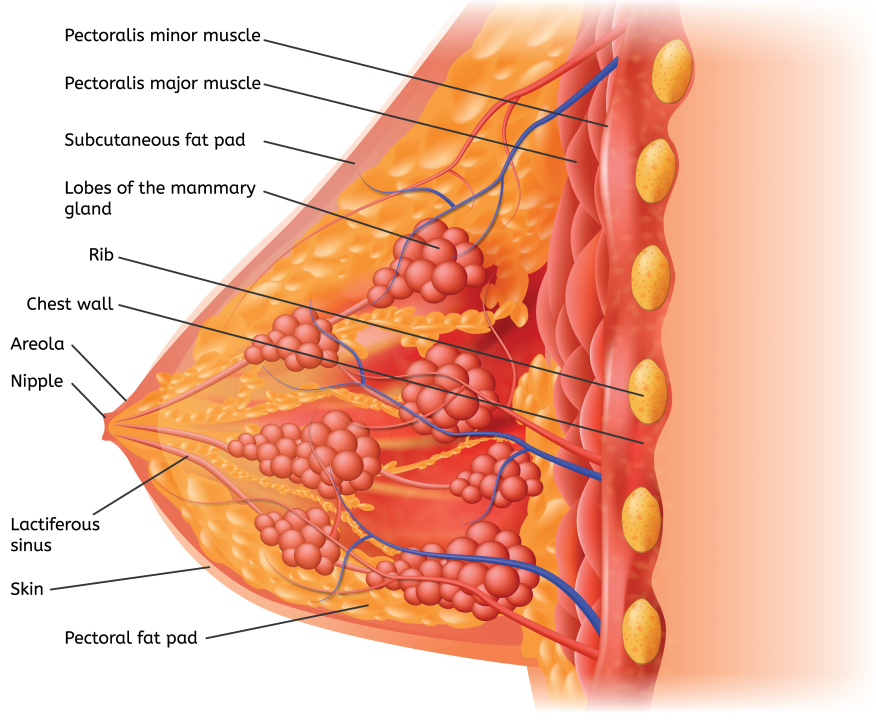

Fig. 1 Anatomy of the human breast. © iStock by Getty Images.

1.2 The history of breast cancer treatment

Throughout history the management of breast cancer has changed dramatically. Medical writings 5,000 years old from ancient Egypt describe breast cancer more frequently than any other cancer form. However, it is unclear whether surgery was a treatment option at that time (3). In ancient Greece, Hippocrates did not consider surgery to be a beneficial treatment because of complications that followed and because of the poor prognosis of the disease. Instead, to prolong life, these tumours were treated with surveillance (4, 5). The first surgical technique was described about 2,000 years ago where excision of the cancer was proposed at an early stage (5, 6). The introduction of general anaesthesia and the use of antiseptics in 1846 and 1867, respectively, revolutionized surgical treatment, enabling more extensive surgery of the breast and making axillary lymph node dissection routine several years later (7).

The contributions of William Halsted (1852-1922) have influenced surgical principles to this day. In 1882, he introduced the classic Halsted radical mastectomy, which involves removal of all breast tissue, the pectoralis muscles and the axillary lymph nodes. The technique was adopted widely,

regardless of the size of the tumour, its type, or the patient's age. However, the extent of the surgical procedure left the patient with a loss of muscle strength and arm function and ruled out the possibility of reconstruction. Halsted referred to this operation as "lifesaving" to justify such destruction of muscles (8). In 1948, Patey (1899-1977) described modified radical mastectomy aimed at preserving the pectoralis major muscle (9), while Auchincloss (1915-1998) and Madden (1912-1999) also developed approaches, which preserved the pectoralis minor muscle (10, 11), along with breast-conserving techniques that dominate the area today.

1.3 Epidemiology

Breast cancer is the most common type of cancer worldwide together with lung cancer and is by far the most common tumour in women, both in high and low income countries. It affects one woman in nine, at some point during their life (12). The number of newly diagnosed breast cancers has increased steadily, but mortality on the other hand has decreased over the past 20 years (13). The incidence rates of breast cancer vary in the world. The highest rates are found in Western Europe and the United States, while the lowest are in Africa and Asia. Breast cancer is the leading cause of cancer-related death among women in less-developed regions and the second most common cause of death in women in more developed regions (12, 14).

In the past few years, nearly 9,400 breast cancer cases per year have been diagnosed in Sweden (15). According to data from the National Quality Register for Breast Cancer (NKBC) in 2020 (16), 8,293 women and 65 men were diagnosed with primary breast cancers, for a total of 8,350 cases (one tumour per breast is reported as one case) (13).

Breast cancer incidence worldwide is associated with the prevalence of breast cancer risk factors. Breastfeeding, which is more common in the developed world, has been found to protect against breast cancer (17). Weight gain after age 18, excess body weight, use of hormone replacement therapy (HRT), physical inactivity, excess alcohol consumption and reproductive/hormonal factors, such as a long menstrual history, recent use of oral contraceptives and null parity or later age at first birth and high mammographic density (18), have proven to increase the risk (17, 19). Breast cancer screening is more common in high-income countries, which also contributes to increasingly higher incidence rates over the past decades (20).

1.4 Tumour classification and histopathology in breast cancer

1.4.1 Breast cancer staging

Modern cancer staging systems provide clinicians with the means to compare groups of patients objectively and to ensure standardized care regardless of treatment. Historically, the anatomical extent of the tumour has been the primary prognostic factor providing the outline for staging and for planning treatment. Although tumour size continues to play a central role, growing knowledge of cancer biology and biomarkers has emerged to make these equally important factors that need to be incorporated into decision making when planning patient care and considering prognosis (21).

1.4.2 TNM classification

The TNM system is a structured tool maintained and revised by the American Joint Committee on Cancer and the International Union for Cancer Control. It applies only to carcinomas and thus there is always a need for histologic confirmation. Stage is defined with an alphanumerical code at different time points of treatment.

> **T** corresponds to the extent of the primary tumour and its relation to surrounding tissues. In the case of multifocal/multicentric primary tumours, the tumour with the highest T value is used for the classification.
> **N** corresponds to the extent of regional lymph node metastasis. The regional lymph nodes are axillary (levels I-III), infra- and supraclavicular, internal mammary and supraclavicular on the ipsilateral side.
> **M** corresponds to the extent of metastasis beyond regional lymph nodes (22).

The prefix c indicates the pre-treatment clinical stage; thus, cT, cN, or cM stages are determined from clinical examinations, radiological imaging, biopsies or surgical exploration.

The prefix p indicates the pathological stage; thus, pT, pN, or pM stages are determined from histopathology of surgical specimens at the primary definitive investigation. Assessment of any residual disease after neoadjuvant treatment can either be made by clinical/radiological examination or by viewing postoperative histopathology specimens (i.e., ycT, ycN, ycM, ypT, ypN, or ypM) (23).

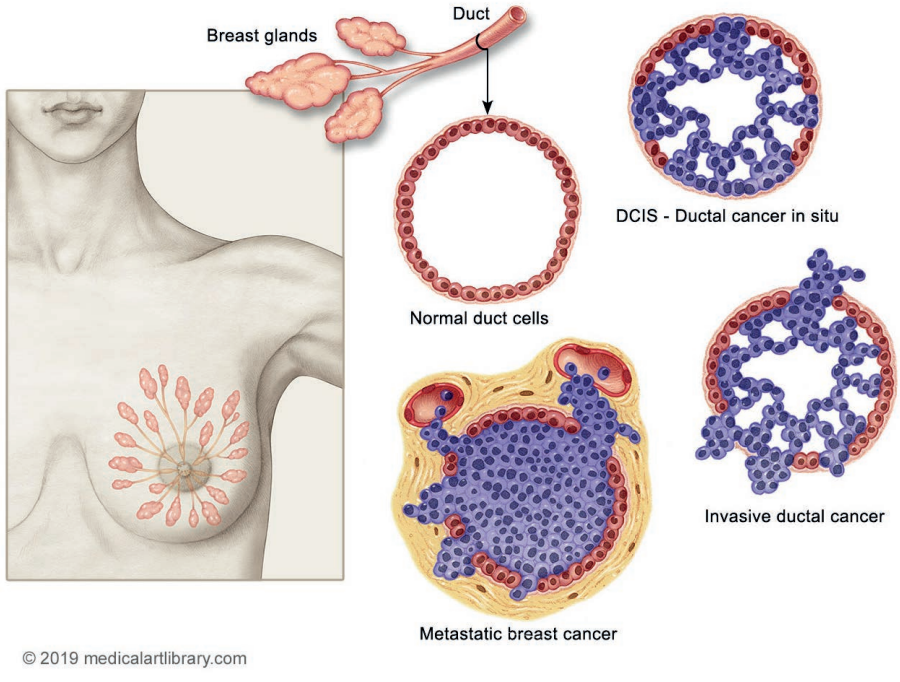

Fig. 2 Development of ductal breast cancer.

1.4.3 Other prognostic criteria

The wider understanding of breast cancer biology in recent years has led to the realization that breast cancers comprise a multifactorial group of diseases, which differ significantly in reoccurrence and survival rates. It is of importance to identify high-risk patients using prognostic criteria such as histopathology grade, the levels and types of hormone receptors and the presence of biomarkers among which human epidermal growth factor 2 (HER 2) and Ki-67 are the more important (24, 25). Deeper understanding of cancer biology and clinical features has resulted in the development of prognostic tools, making it possible for clinicians to provide a precise individual prediction of outcome (26).

1.4.3.1 Histopathology grade

Bloom and Richardson established histopathology scores reflecting the degree of malignancy and prognosis for breast tumours (27). The proportion of tubule formation, the extent of nuclear pleomorphism and the mitotic count using a defined field area are scored I-III. The total sum translates to the grade of each carcinoma (28). However, there are some concerns about the reproducibility of the system and subsequent studies have stressed the need for multidisciplinary assessments to increase its reliability (29, 30).

1.4.3.2 The oestrogen receptor

The oestrogen receptor (ER) is overexpressed in more than 70% of breast cancer cells. Thus, 17-oestradiol activates the ER, which induces tumour growth and inhibits apoptosis of tumour cells (31, 32). The presence of the ER is important in the clinical management of breast cancer and is shown to have prognostic impact in predicting response to adjuvant endocrine treatment (33). Forty percent of ER-positive tumours are resistant to tamoxifen, which can explain why endocrine therapy in certain patients remains ineffective (34, 35). At present, ER assessment is made on formalin-fixed, paraffin-embedded breast cancer tissue using immunohistochemical (IHC) staining (36). Many European countries including Sweden use the threshold of 10% stained nuclei when a tumour is graded as ER-positive (37). The American Society of Clinical Oncology/College of American Pathologists advocate a 1% threshold for positivity because tumours with only 1% positivity for the ER respond to HRT (38). ER-positive breast cancers have better prognosis probably because of generally slower proliferation compared with ER-negative cancers. However, recurrence-free survival is thought to be the same about 15 years after diagnosis. This implies that ER status might have little significance for the establishment of micrometastases before diagnosis (39, 40).

1.4.3.3 The progesterone receptor

The progesterone receptor (PR) is a positive prognostic factor in the presence of the ER because it is mediated by oestrogen. The PR is associated with a favourable response to endocrine- and chemotherapy and is usually evaluated using IHC (41, 42). Tumours that are both ER- and PR-positive have about a 70% chance of responding to endocrine therapy of any type, while tumours that are ER-positive and PR-negative respond in about 20-40% of cases. The chance of responding to endocrine treatment in an ER-negative and PR-positive tumour is 40-45% and tumours that are both ER- and PR-negative have less than a 10% chance of a favourable endocrine response (43, 44). However, there are data questioning the clinical importance of PR as a predictor and there is an ongoing debate about its clinical usefulness. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group found that the PR status had no additive value in the response to tamoxifen by ER-positive cancers (39).

1.4.3.4 Human epidermal growth factor receptor 2

Human epidermal growth factor receptor 2, (HER2 or ErbB2) is a plasma membrane-bound tyrosine-protein kinase receptor (45). It is normally involved in cell proliferation and division, but if amplified in a malignant breast cell, it is a predictive factor associated with more advanced disease, more likely to relapse and lead to shortened patient survival (46). HER2 amplification is present in approximately 15-30% of breast cancers (47). HER2 is

assessed using IHC, but when the results are equivocal, specimens should undergo confirmation with fluorescence in situ hybridization (FISH) analysis (47). Chromogenic in situ hybridization (CISH) assay can provide an accurate and practical alternative to FISH with a concordance of 98.4% (48). Polymerase chain reaction (PCR) amplification is also recommended for indeterminate cases (49).

1.4.3.5 Ki-67

Ki-67 is a protein found in cell nuclei and expressed during proliferation. Therefore, a Ki-67 monoclonal antibody is used as a marker for cell division and is considered as a negative prognostic marker for cancers. Several studies have shown that the proportion of Ki-67-positive tumour cells is associated with lower overall survival (OS) among patients and tumour recurrence (50, 51). However, high Ki-67 levels in certain types of tumours could also be indicators of a good response to chemotherapy (52).

1.5 Histology

1.5.1 Carcinoma in situ of the breast

In Sweden, 10.9% of all diagnosed breast cancers were judged non-invasive in 2020 (16). Ductal carcinoma in situ (DCIS) has malignant epithelial cells confined within the ducts without invasion of the surrounding tissue through the basal membrane and hence does not metastasize (53). The lesions are classified according to differentiation and growth – low-, intermediate- and high-grade DCIS – which correlate with the clinical course of the disease (54). With the introduction of screening mammography (MG), the numbers of patients diagnosed with DCIS have increased dramatically. One in every 1,300 screening mammograms is positive for DCIS. Only 13% of DCIS cases are symptomatic, presenting with a palpable lump, nipple discharge or Paget's disease of the nipple. Bilateral DCIS is present in 20% of those diagnosed with DCIS (55). At present, it is uncertain how likely DCIS is to develop into a truly invasive cancer with time. It is understood that in the absence of treatment, these changes do not always occur because of differences in genotype that prevent progression (56). Studies show that DCIS is present in up to 15% of autopsies, confirming that this could be present and asymptomatic without progression into a true carcinoma for long periods (57). In one study, gene expression patterns in DCIS and invasive cancers were classified into intrinsic molecular subtypes defined for invasive breast cancer to identify the risk of progression of DCIS into an invasive cancer. This knowledge could potentially prevent under- and overdiagnosis (58). The consequences of overdiagnosis are significant, namely unnecessary surgical treatments and negative effects on psychological well-being and quality of life. The excess of breast

cancer incidence comparing screened and unscreened women was studied in the Malmo trial in a 15-year follow-up. The rate of overdiagnosis of breast cancer was 10% in the group of women aged 55-69 years when compared with controls who were never screened (59). Some women die of breast cancer without first receiving a diagnosis of locally invasive disease, which raises the question of whether DCIS has malignant potential from its onset (60-62). Narod et al. published a study (n = 108,196) to estimate the patient mortality rates from breast cancers following a diagnosis of DCIS. They found that the 20-year breast cancer-specific mortality rate following a diagnosis of DCIS was 3.3% and that women with African origin and younger women were at higher risk. They concluded that DCIS should in fact be considered as a breast cancer, not as a precancerous marker and that prevention of ipsilateral invasive recurrence did not prevent deaths from breast cancer. However, the study had some methodological flaws such as not being able to distinguish between screening-detected and symptomatic DCIS or which patients were on adjuvant tamoxifen treatment (63).

Several long-term studies have shown that 20-53% of patients with earlier misclassified DCIS biopsies present with an invasive carcinoma over a 10-year period or more (64-68). The size of the DCIS lesion is associated with the risk of local recurrence. However, it is difficult to appreciate the extent of DCIS because of the growth pattern in the ductal branches of the breast parenchyma. As DCIS is considered a precancerous lesion, it often requires the same treatment as invasive carcinomas. Excising the lesion with adequate margins is important because positive or close-to-positive margins are also associated with an increased risk of recurrence (69-71). Patients with DCIS undergo local treatment with breast-conserving surgery (BCS) and supplementary radiotherapy or – for large tumours – mastectomy. Several randomised trials and notably the Swedish DCIS trial confirmed that patients with high-risk DCIS treated with BCS have greater benefit from radiotherapy (RT) in terms of reduced risk of recurrence than those without RT (72, 73). Lobular carcinoma in situ (LCIS), also known as lobular neoplasia, is viewed as a risk factor and a non-obligate precursor lesion. When compared with the general population, women with LCIS have a 9-10-fold increased relative risk of developing DCIS or an invasive carcinoma. Surgical excision is rarely necessary provided imaging and histopathological results support the diagnosis. Active surveillance is the most common management option (74).

1.5.2 Invasive breast cancer

Invasive breast cancer is a heterogeneous group of diseases that have in common the invasion of malignant cells into the surrounding tissue. According to the new definitions, the previously known invasive ductal carcinoma (IDC), is now referred to as invasive carcinoma of no special type (NST). This is the largest group accounting for 70-80% of all diagnosed primary breast cancers

and the diagnosis is made by exclusion of other specific types of breast cancer (75). The most common specific subtypes are invasive lobular (5-15%), tubular (2%), medullary (1-7%), mucinous (2%), invasive papillary (1-2%), and metaplastic (1%) carcinoma (76). The definition of these tumours is based on their histological morphology and they exhibit a variety of particular clinical and prognostic features (75).

The clinical symptoms of inflammatory breast cancer differ from non-inflammatory cancer (75). Inflammatory breast cancer accounts for 2% of all breast cancer. The histopathologic features are distinctive including lymphatic tumour cell emboli in the skin of the breast. Some data imply that inflammatory breast cancer often is NST grade III while other say that it histologically may be an entirely different cancer form (75, 77). The inflammatory breast cancer often expresses HER2, lack the expression of ER an PR and has an overexpression of less favourable biomarkers which contributes to a poor prognosis (28, 78).

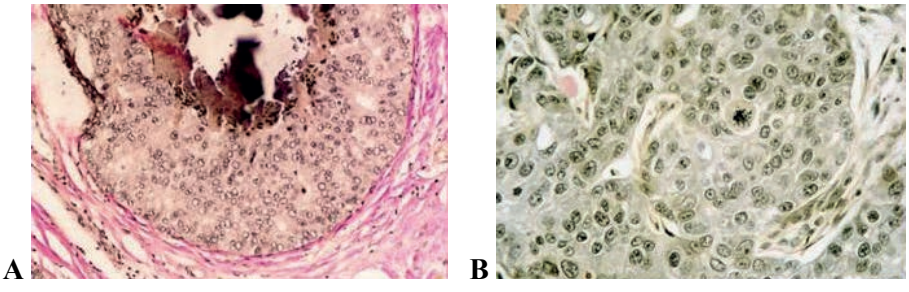

Fig. 3 Histopathological images of A. high grade DCIS and B. invasive ductal breast cancer. By courtesy of Dr Staffan Eriksson.

1.5.2.1 Intrinsic molecular subtypes

Breast cancers are no longer considered a single disease and their complexity is not fully reflected by the above-mentioned main clinical parameters and histopathological molecular markers. All of these parameters are routinely used in daily practice to select treatment and predict prognosis but with the advancement of gene expression profiling five main intrinsic molecular subtypes of breast cancer (Luminal A, Luminal B, HER-2-enriched and a basal-like and normal breast-like group) have been identified (79-83). Gene expression profiling is expensive, time-consuming and might require a fresh tumour sample not fixed in formalin (84). Therefore, efforts have been made to utilize IHC analysis to create approximated subtypes; however, the overlap is not exact (85). During the 12th St. Gallen International Breast Cancer Conference (2011) the expert panel adopted an intrinsic subtype-based approach for recommending adjuvant systemic therapies (86).

In most studies, the dominating group consists of ER-positive tumours and is further divided into two subgroups, luminal types A and B, both dominated

by genes normally expressed by luminal breast epithelial cells. Thirty to 40 percent of all invasive breast cancers are luminal A tumours and they are thus the most common. Most are well-differentiated NST carcinomas, lobular, tubular, mucinous, neuroendocrine or cribriform carcinomas (87). A luminal A tumour is generally associated with a more favourable prognosis (88) and presents less frequently with extensive lymph node involvement (89, 90). Earlier, the cut-off point of Ki-67 level to separate luminal A from B subtypes was set at 14% (91), but more recently, this was changed to 20% (92). Luminal B tumours generally have higher expression of genes involved in mitosis, cell proliferation (93) and are not as well differentiated. Luminal B breast cancers characteristically do not overexpress HER2, but approximately 30% of them will be HER2-enriched. The separation of luminal A from B tumours is important because the luminal B molecular subtype is associated with a more intermediate prognosis (94). Luminal B tumours comprise 20-30% of all invasive breast cancers, mostly invasive NST carcinomas (87), and have higher recurrence rates (St. Gallen 2013) (95).

The other main molecular subgroup comprises ER-negative tumours, which often have two subgroups. One is the HER2-enriched group characterised by a high expression of HER2-related genes. HER2-positive tumours are less frequent than the others, at 12-20%. They are less-differentiated infiltrating NST carcinomas, apocrine and pleomorphic lobular carcinomas. Historically, high levels of HER2 have been associated with a worse prognosis based on studies where patients were not treated with HER2-targeted therapy (96). More recent trials including patients with HER2-positive tumours receiving targeted drugs, including trastuzumab and pertuzumab, have been shown to modify the natural course of HER2-enriched tumours, resulting in improved outcomes (97).

HER2-negative tumours belong to a group of ER-negative tumours, namely triple-negative breast carcinomas (TNBCs), generally expressing genes typical of basal epithelial cells and are therefore called basal-like. Basal-like tumours are the most diverse and share the fewest similarities with the other groups. They represent 15-20% of all invasive breast cancers. They have the least favourable prognosis, with a high incidence of distant metastases. Paradoxically, the prognosis becomes better by 5 years after the initial diagnosis (98, 99).

Normal-like tumours comprise the last group of non-luminal tumours and have gene profiles like those found in normal breast tissue (100).

1.5.2.2 Lymphatic Invasion

Lymphatic vessels were formerly not considered to play an important role in the dissemination of breast cancer cells, but are now regarded as the main route by which tumour cells reach axillary lymph nodes (101-103). The presence of lymph vessel invasion is associated with an increased risk of regional lymph node and distant metastases (104), and is an independent predictor of

lymph node metastases in breast cancers. Some studies have demonstrated that high lymphatic vessel density in primary breast cancers is also an unfavourable prognostic factor (105, 106).

1.6 Breast imaging

Today the conventional diagnostic tools include clinical evaluation of the breast, MG, ultrasonography (US), fine needle and/or core biopsies (107). The prognosis for women with breast cancers has improved mainly thanks to early diagnosis, multidisciplinary approach and more effective treatments (108).

1.6.1 Mammography

In the diagnostics of early breast cancers conventional or digital mammography (MG) is considered gold standard. It is estimated that 700.000 mammograms are performed each year in Sweden at a cost of 400 million SEK (109). X-ray imaging for MG uses low-dose ionizing radiation to create detailed images of the breast. To reduce this dose and immobilize the breast, it should be compressed. In that way, all tissues are imaged and examined. A limitation of MG is its poor sensitivity, which is only 75-80% and possibly less than 30% in the population of younger women with subtle lesions in dense glandular tissue (110). The sensitivity for detecting multiple malignancies could be less than 50% (111).

The European Society of Breast Cancer Specialists (EUSOMA) suggests that 90% of malignant findings should be confirmed by image-guided biopsies and breast pathology histologically prior to surgery (112). The increase of breast cancer risk because of exposure to ionizing radiation from repeated MG examinations has been debated widely. Breast cancer gene (BRCA) mutation carriers are subjected to regular imaging (see below) and could be more sensitive to the negative effects of radiation, although the results are inconsistent.

1.6.1.1 Screening

MG as a screening tool emerged in the 1960s. Screening MG is performed in asymptomatic women and its aim is to detect any breast cancer at an early stage before the tumour is palpable, to improve chances for a successful treatment and prognosis (113). Cancers detected on service MG screening are more likely to have smaller size, be node negative and better differentiated when compared with symptomatic cancers (114). Also, with the correct diagnosis and estimation of size, character and localization of a lesion, the chances of correct treatment choice increase, reducing the risk of reoperation rate and improvement of survival (115). The randomised Swedish two-county trial reported in women aged 40-74 years a 31% reduction in breast cancer-specific mortality rate when screening MG was offered (116). A follow-up after 29

years showed that the relative benefit from MG screening has remained stable during all this time (117). Thus, screening MG is considered the only breast imaging modality that reduces breast cancer mortality (118). Additionally, MG has become an established method, also proven to be cost effective (115).

Overdiagnosis has been the main issue of debate regarding MG screening. Critics argue that some of the detected and treated cancers might never have progressed to life-threatening disease in the absence of screening MG (119). Furthermore, patients are forced to experience radiation exposure and the physical and psychological effects of further investigation of suspicious findings (120). Nevertheless, MG screening is recommended in most European countries where it is concluded that the benefits outweigh the risks (121). Health-care systems worldwide lack the resources for population-wide MG screening programs, so awareness of early signs and symptoms and clinical breast examinations are the recommended approaches (122).

1.6.1.2 Breast density

Screening using MG misses about 15% of all breast cancers, most often because of high density, namely variations in the composition of breast tissue, which can obscure a noncalcified lesion. MG has a low contrast resolution in women with dense breasts which makes a potential tumour difficult to differentiate from dense breast tissue (123).

There are several ways to describe mammographic breast density using MG. The American College of Radiology Breast Imaging-Reporting and Data System (ACR BI-RADS) 5th edition classifies breast density into four subcategories: A ("almost entirely fatty"); B ("scattered areas of fibroglandular density"); C ("heterogeneously dense breasts, which may obscure small masses"); and D ("extremely dense breasts, which lowers the sensitivity of MG"). The previous ACR BI-RADS edition described the density in percentages, but this was replaced with less subjective grading (124).

Mammographic breast density is known to be a strong and established risk factor for breast cancer. Women with dense breast tissue have a 4-6-fold increased risk for breast cancer (18, 125-127) and these tumours present with more aggressive characteristics, such as large tumour size and high grade (128, 129). Whether density may also be associated with certain molecular tumour subtypes compared to women with predominately fatty breast tissue, is still controversial (130-134).

Breast magnetic resonance imaging (MRI), when used with a contrast agent is a more sensitive method than MG in detecting early breast tumours in women with dense breasts. A large Dutch randomised multicentre study of 8,000 patients with dense breasts has been published and MRI was evaluated for the occurrence of interval cancer within 2 years. Patients offered MRI as a complement to MG screening, were compared with 32,000 patients in the control arm screened using MG alone. Interval cancer during the 2-year period was noted in 2.5 per 1,000 examinations among those invited to undergo MRI

(including the 41% who declined the study). In those who were offered MRI and participated in the study, the frequency was 0.8 per 1,000 examinations. Among non-participants in the MRI group there were 4.9 interval cancers per 1,000 similar to the 5.0 per 1,000 among those who only received MG. Survival data have yet to be presented in that study (135).

1.6.2 Ultrasonography

Recommendations from the American College of Radiology state that MG is the first choice for screening all women. Ultrasonography (US) should be considered in high-risk patients who cannot tolerate MRI, in patients with moderately dense breasts, or to differentiate cysts from solid masses. According to a multicentre trial conducted by Berg et al. screening breast US detects 4.2 additional cancers per 1,000 women with normal mammograms (136).

Supplemental use of US with MG is required and can strengthen the diagnostic precision especially when used in interventional procedures. A strength is that US is well tolerated by patients and is radiation-free. US is widely available and relatively inexpensive but when used as a single modality it has limited value, as it is less sensitive in visualizing microcalcifications and less reproducible than other techniques (137). It also requires an experienced physician to perform the examination (138).

When there is no convincing palpable mass, the combination of a normal MG and a normal US has a negative predictive value greater than 98%. The use of US as an adjunct to MG can increase accuracy by up to 7.4%, but there have been no randomised control trials assessing long-term benefits such as survival associated with screening US (139).

1.6.3 Breast Tomosynthesis

New modalities such as breast tomosynthesis can contribute to further improvements in breast cancer imaging. It is an advancement of the MG technique, that compresses the breast to acquire images at multiple angles during low-dose x-ray exposure. The images are reconstructed into a three-dimensional (3-D) image of the entire breast displayed as thin slices individually or continuously.

Compared with two-view digital MG, 3-D breast tomosynthesis had higher sensitivity at a slightly lower specificity for breast cancer detection (140).

1.6.4 MRI

The Nobel Prize in 1952 was awarded to researchers for the discovery of nuclear magnetic resonance. This breakthrough eventually led to the development of MRI.

Human breast images were some of the first produced using MRI (141). However, during the 1980s MRI lost its popularity when it came to diagnosing breast cancers. It would take some years until MRI returned with the application of contrast agents and its enhancement of tumours in comparison with surrounding tissue (142).

MRI is now emerging as an increasingly important diagnostic tool with improved techniques. It provides information on tumour morphology in cross-section but also functional information on tissue perfusion and enhancement kinetics. The development of an MRI coil specifically designed for breast imaging and the use of gadolinium contrast agent are important advancements, which require creatinine testing prior to administration (143, 144).

Enhancing lesions are assigned to three main categories: focus/foci, masses and areas of non-mass enhancement. A focus is described as a tiny spot of enhancement usually smaller than 5 mm, often too small to characterize further. Multiple foci are typically seen in the fibrocystic breast, although a very small carcinoma can appear as a focus. A mass is a 3-D lesion that is space-occupying and can be described further in terms of size, shape, margin and enhancement characteristics. Abnormally enhanced tissue within normal fatty or glandular tissue is described as non-mass-like enhancement. This area is thus not described as a 3-D area or a mass but is seen as a disruption in the normal tissue pattern most often seen in benign diseases but also in cases of DCIS (145).

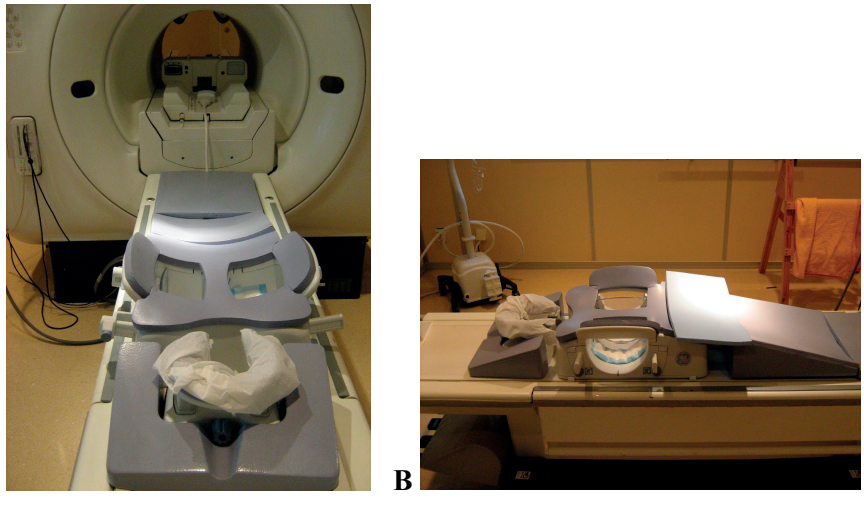

Fig. 4 A. MRI scanners use a strong magnetic field and radiofrequency pulses to create high resolution images. B. A dedicated double breast surface coil is essential to permit simultaneous high-resolution and high-quality imaging of the breasts. By courtesy of Dr Anders Karlsson.

The contrast uptake characteristics during contrast medium injections of invasive tumours differ from benign lesions. The rate of contrast uptake by the

lesion during the early phase, the first 2 min after contrast administration, can be described as slow, medium or rapid with specific thresholds (146). The rest of the curve is the delayed phase. As a result, contrast use results in three different types of enhancement, persistent type I, plateau type II and wash-out type III (147). A slow, continuous enhancement curve is seen in a non-malignant lesion and an enhancement followed by a plateau can be attributed to an either benign or malignant lesions. Finally, due to increased vascular permeability, density, and interstitial fluid there is a fast initial enhancement followed by a wash-out in malignant lesions (148).

Multiple studies have shown that MRI is more sensitive (89-100%) than MG in detecting primary breast cancers (149, 150). But breast MRI is a modality most reliable if correlated with MG and ultrasound and is thus a good complement in order to sharpen the diagnostic abilities. The sensitivity for multifocal cancer is 90-100% compared to 12-46% for MG and 30% for US. Tumour extent is often more accurately described with MRI than with MG and US and the sensitivity for contralateral disease is 88-100% as opposed to 19-56% with MG (151-154). MRI also has an advantage over MG and US when imaging both breasts and the chest wall (155).

Thus, the detection of small malignant lesions with MG is impaired by dense fibroglandular tissue (156). There is evidence implying that women with dense breasts treated with breast conservation more often face the risk of conversion to mastectomy because of occult disease. A study showed that women with dense breasts had a 4-fold higher rate of local recurrence compared with women with low-density breasts (157). Contrast-enhanced MRI surpasses MG in diagnosing breast cancers in dense breast tissue but the degree of parenchymal enhancement with gadolinium-based contrast medium should be accounted for, as it might affect the accuracy of estimating tumour size (158). In addition, creatinine testing is required prior to the administration of gadolinium contrast requires due to renal elimination (159).

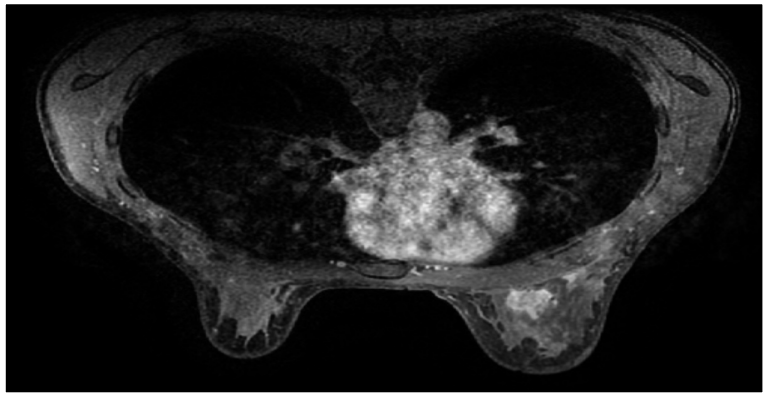

Fig. 5 Breast MRI image showing a 2 cm malignant lesion close to the chest wall on the left side. By courtesy of Dr Anders Karlsson.

The specificity of MRI for detecting gadolinium-enhanced enhanced lesions is reported to be suboptimal, 65-84% (160, 161). Because benign lesions also undergo such enhancement, they contribute to the high number of false positive findings. These findings very often require confirmation with MRI- and US-guided procedures. However, until recently MRI-guided biopsies were not possible because of technical difficulties (162). In premenopausal women it is important to take the menstrual cycle into consideration when performing an MRI examination because contrast medium uptake is dependent on the phase of the menstrual cycle. MRI should be performed only during days 7-14 in the menstrual cycle, otherwise endocrine factors might result in false positive findings. Other factors such as hormone replacement therapy (HRT), lactation and radiation therapy to the breast could increase background enhancement, whereas tamoxifen treatment could decrease it (146).

An invasive lobular cancer (ILC) normally does not form palpable lumps because of lack of calcification, necrosis, or haemorrhage within the tumour (163, 164). Hence, ILC is difficult to diagnose clinically and with conventional diagnostic imaging. Mastectomy rates are also possibly higher in women with ILC than in other types, which reflects the diffuseness of the tumour, multifocality and the tendency for occult involvement of the contralateral breast (165-167). Therefore, the UK National Institute for Health and Clinical Excellence (NICE) guidelines currently recommend MRI in patients with ILC considering BCS. MRI has proven to better correlate with size measurements at histopathology than MG and US (168, 169) and more often shows additional multifocal lesions and occult contralateral disease leading to changes in management in close to 30% of the cases (168, 170). In a prospective cohort study, 72 consecutive patients with ILC undergoing breast MRI, there were 19 additional findings, leading to a change in management strategy in 26.4% of cases. The final rate of mastectomy was 36.1% and the reoperation rate in those patients receiving BCS was 18.3%. The accuracy of MRI was better than that of MG and US. During a follow-up duration of 44 months the disease-free survival (DFS) was 95.8% and overall survival (OS) rate was 98.6% There were no survival data reported from patients undergoing MG/UL alone for comparison (171).

In the past, MRI was not considered effective in the assessment of DCIS (172, 173). It has now been demonstrated in several studies that MRI is the most sensitive imaging tool for detection of all grades of DCIS due its variation in vascularity and thus differentiating the most clinically relevant DCIS lesions (174, 175). Other studies have shown MRI to more be reliable in predicting the extent (176-178) of DCIS disease as well as any underlying invasive component (179).

The most common mammographic appearance of DCIS is microcalcification, but noncalcified lesions, particularly in dense breasts are not easily detectable by MG. MRI relies on contrast enhancement for the detection of breast cancers and is thus not limited by dense breast tissue. DCIS presents

with non-mass enhancement on MRI in 60-81% of cases, a mass in 14-41% of cases or a focus in 1-12% (180-182). The addition of kinetic enhancement assessment of MRI further improves its ability to distinguish benign lesions from those with malignant appearance (72, 183).

1.6.5 Indications

1.6.5.1 Staging before treatment planning

Numerous studies show that new information on multifocality, tumour extent or contralateral findings is gained by preoperative breast MRI, which can alter the preliminary treatment plan (e.g. conversion from BCS to mastectomy or a suggestion of wider margins in BCS) (161, 184, 185). Published data confirm the benefit of biopsy for MRI-detected lesions in order to reduce overtreatment caused by false positive findings (162). Several studies associate the use of MRI with an increased mastectomy rate (186, 187). Another reported disadvantage is the increase in lead time from diagnosis to treatment compared with standard care, related to preoperative breast MRI and the need for additional procedures (188).

A meta-analysis with data from 19 studies reported change in treatment plan in 16.6% of the included patients undergoing preoperative MRI (155). Another retrospective cohort study reported MRI-induced treatment changes in 11% and a reoperation rate of 14% in an MRI group compared with 20% among patients having no-MRI, although the difference was not statistically significant due to lack of power (189).

Evidence supporting preoperative breast MRI from a longer perspective regarding recurrence and survival rates has been varied in terms of quality and results. In a cohort study where 215 patients underwent preoperative breast MRI and 541 did not, there was no reduction in the tumour recurrence rate when MRI was performed, in terms of contralateral cancer, nor in cause-specific survival. However, the study was criticized because of some methodological flaws (186).

In another study in South Korea by Yi et al. (n = 936), patients with breast cancer and preoperative MRI were matched with a group without MRI. Unilateral MRI of the breast was performed during the first time period and bilateral MRI was used during the second one. There was no difference in re-excision rates between the MRI and control groups. However, after a follow-up period of five and a half years, total DFS was better and contralateral disease rates were lower in the group that receiving bilateral MRI, which supports the need for examination of the contralateral breast. No differences were found in locoregional recurrence or distant recurrence rates between the two groups. In the group where MRI was done unilaterally, reduced locoregional recurrence rates was observed, which can be explained by an MRI protocol

resulting in better spatial resolution and thus more accurate mapping and potentially more precise surgery (190).

There are only three published prospective randomised studies apart from our reported preoperative MRI of the breast (POMB) study (Paper I) (191) investigating the clinical efficacy of preoperative breast MRI compared with triple assessment alone, and the results were inconclusive. The Comparative effectiveness of MRI in breast cancer (COMICE) multicentre study included 1,623 women with biopsy-proven breast cancer planned for BCS. Patients were randomised (n = 816) to preoperative MRI as an adjunct to conventional assessment, or to a control group managed with standard of care (n = 807). There was no statistically significant difference in the reoperation rate between the two groups: 19% in the MRI group vs 19% in the control group. Furthermore, there was no significant reduction in the mastectomy rate in the MRI group (192). In the MR mammography of nonpalpable breast tumours (MONET) study, 207 patients with non-palpable BI-RADS grade 3-5 lesions were randomised to have preoperative breast MRI apart from triple assessment and 211 were randomised to triple assessment alone. Only 36% of patients included in each group had confirmed malignancy and the reoperation rate was in fact higher in the MRI group. The number of conversions to mastectomy did not differ significantly between groups (193). In the third study, 100 patients with stage I breast cancer were included, and half were randomised to each group. Among the patients randomised to preoperative MRI, there were additional findings altering the management plan for 20% of them but these had no impact on the reoperation rate. There was no difference in the definitive mastectomy rate between the groups (194).

1.6.5.2 MRI screening in breast cancer gene mutation carriers

Breast cancer in women with an inherited mutation in BRCA1 and BRCA2 (BReast CAncer gene) account for about 3% of all breast cancers (195). BRCA1/2 mutations, predispose female carriers to a cumulative risk by age 80 years of 50-60 percent (196). Hereditary breast cancer differs from sporadic breast cancer in terms of age at diagnosis, morphology, and the presence of specific biomarkers (197-199). As prevention, these women can choose total mastectomy as a risk-reducing procedure, which is the most effective way to reduce the incidence of subsequent breast cancers (200). The high sensitivity of MRI in detecting breast cancers compared with conventional imaging techniques has prompted the American Cancer Society to recommend annual MRI screening to women with a lifetime risk greater than 20-25% (201). Surveillance programs for this group of patients are a well-accepted option instead of risk-reducing surgery. Breast MRI screening is also recommended to patients who have received mantle radiotherapy before 30 years of age. The sensitivity of MG is often insufficient to detect breast cancers in women with lobular intraepithelial neoplasia, atypical ductal hyperplasia, high breast density, and

earlier diagnosed breast cancers. These women have a risk of 15-20% for developing breast cancers (201).

1.6.5.3 Occult primary breast cancer

Axillary lymphadenopathy is the first presenting symptom of breast cancer in 0.3-1.0% of women (202, 203). Occult breast cancer is not evident on MG or US, nor during clinical examinations. Detection and localization of the primary tumour is important for staging and subsequent treatment planning (204). MRI with its high sensitivity is frequently used when MG and US fail to find the primary source of a tumour in the breast (205). Data from 10 trials have shown that MRI can detect occult breast tumours in 35-100% of patients (206).

1.6.5.4 Breast cancer recurrence

When patients are treated successfully for breast cancers, they should be monitored regularly with the intention of discovering relapses or new primary tumours at an early stage. Most guidelines recommend routine physical examinations and MG for at least 3-5 years after cancer treatment (207). In some circumstances, additional imaging with MRI is indicated in an early phase after surgery and/or RT (208). MRI appears also to be valuable in differentiating post-treatment changes from breast cancer recurrence (209).

1.6.5.5 Evaluation of response to neoadjuvant chemotherapy

Neoadjuvant chemotherapy could be administered to reduce the size of a large tumour and the extent of local surgery needed. This is reported to reduce the tumour in approximately 80% of such patients, making curative surgery possible and reducing the risk of local recurrence (210, 211). A meta-analysis based on 11 trials showed that BCS was chosen by 28-89% of patients after neoadjuvant chemotherapy (212).

Breast MRI has proven to be superior compared with clinical examinations and conventional imaging in the evaluation of breast cancer response to neoadjuvant chemotherapy, because of its high ability to image the chest wall and the surrounding tissue such as the skin and axilla (213). Studies have shown that the prognosis for patients is similar whether chemotherapy is given before or following surgical intervention. However, the neoadjuvant setting is advantageous when the tumour response can be monitored continuously (214).

1.6.5.6 Patients with breast augmentation or reconstruction

MRI can be used to evaluate implant integrity in women with breast implants used for augmentation for cosmetic reasons or reconstructive purposes. The risks of silicone-filled breast implant rupture vary with the manufacturer, type of implant and indication for surgery and a rupture rate of 1-2% over 6 years is reported (215). MRI can detect a rupture in 78-89% of affected women vs only 25-30% with MG (216-218). MRI can also be used to assess the extent

of intra- or extracapsular silicone leakage or the presence of granulomas. US and MRI are recommended as imaging modalities complementary to MG when evaluating a potential breast cancer in symptomatic women with breast implants when MGs are negative (206).

1.6.5.7 Inflammatory breast cancer

Inflammatory breast cancer accounts for about 2% of all cases. There is often a delay in diagnosis because the main clinical presentation simulates mastitis. MRI is useful to eliminate or confirm the diagnosis of inflammatory breast cancer after an ambiguous biopsy or to evaluate the treatment response after using antibiotics to treat mastitis (219).

1.6.5.8 Nipple discharge

The incidence of malignancy or premalignant pathology is 15% when a woman presents with symptoms of persistent, unilateral, single-duct nipple discharge. Investigations with MG and US are indicated, but it is reported that up to 10% of these examination results could be false negatives (220). However, evidence of the role of breast MRI in this clinical setting is insufficient. MRI is a viable option for those patients refusing ductography or when technical reasons prevail (206).

1.6.5.9 Characterization of equivocal findings at conventional imaging

When conventional imaging is equivocal, non-diagnostic breast MRI should be performed for enhanced diagnostic accuracy (221).

1.7 BI-RADS

In addition to BI-RADS for MG, the American College of Radiology has defined a Breast Imaging MRI Lexicon and a Reporting System specific for the interpretation of MR imaging. It contributes to a standardized terminology of breast imaging findings, adding structure to the report and classifying the findings. The purpose is to correlate these findings with the clinical history and examination of the patient as well as to conventional imaging, to convey accurate information to other clinicians involved in the management of the patient. The BI-RADS reporting system classifies the MRI findings into seven categories of which five give a practical description as follows (146).

- BI-RADS 0: *incomplete*
  - Additional imaging evaluation is needed.
- BI-RADS 1: *negative*
  - No abnormalities are found. Follow-up with routine breast MRI screening if the cumulative lifetime risk ≥ 20%.
- BI-RADS 2: *benign*
  - Benign findings such as non-enhancing fibroadenomas, cysts, scars, and lipomas. Follow-up with routine breast MRI screening if the cumulative lifetime risk ≥ 20%.
- BI-RADS 3: *probably benign*
  - Findings with very high probability of being benign. The recommendation is for short interval (6 months) follow-up.
- BI-RADS 4: *suspicious*
  - Findings that do not have classic appearance of malignancy but are sufficiently suspicious to justify a recommendation for biopsy.
- BI-RADS 5: *highly suggestive of malignancy*
  - Findings with a very high probability of malignancy. Tissue diagnostic tests are recommended.
- BI-RADS 6: known biopsy-proven malignancy
  - MRI for cancer staging or evaluation of neoadjuvant chemotherapy.

1.8 Multi-disciplinary team (MDT) approaches

The theory that patients with early breast cancers could develop metastases when tumour cells are undetectable at the time of diagnosis contributed to a shift in breast cancer management, and systemic therapies began to be used in patients with early-stage disease (222). As a result of the ongoing advancements in breast cancer diagnosis, staging and management, treatment plans are becoming more complex (223). The expertise of all involved specialists and a forum for effective discussion is essential to develop an optimal treatment strategy (224). To make such communication possible, MDT conferences should gather to discuss each patient. Each specialist contributes independently according to their expertise to the diagnostic and treatment decisions regarding the patient (225). The aim of MDT meetings is to provide patients with consistent, continuous, coordinated and cost-effective care that is evidence-based (226). There is evidence that MDT conferences contribute to a shorter mean time from diagnosis to treatment (29.6 vs 42.4 days; $P < 0.0008$), increased patient satisfaction and a higher proportion of patients receiving neoadjuvant chemotherapy or lumpectomy alone (227). Importantly,

there are studies that show that MDT referrals result in altered treatment recommendations for 43% of patients (227).

1.9 Breast cancer treatment

The diagnosis and treatment of invasive breast cancer requires collaboration among all involved specialties. In those patients who present with operable lesions, the type of surgical resection and systemic therapy can be varied in different combinations. Preoperative adjuvant therapies can be used to downstage the tumour, resulting in a more favourable tumour-to-breast ratio, allowing less extensive surgery.

1.9.1 Surgery

1.9.1.1 Mastectomy

There are several options when choosing the less aggressive modern mastectomy, involving removal of only the breast: total or simple mastectomy, skin-sparing mastectomy and nipple/areolar-sparing mastectomy. The choice of method depends on tumour characteristics and/or patient preferences to undergo immediate breast reconstruction using tissue coverage with expander/implant or autologous tissue flaps. Several studies have assessed the oncologic safety of skin-sparing mastectomy, with local recurrence rates that vary up to 7%, like those observed for simple total mastectomy (228-231). Local recurrence of tumours following nipple/areolar-sparing mastectomy are reported to be 2-5% after a median follow-up of 2-5 years (232-235).

Nipple/areolar-sparing mastectomy is an option for patients undergoing prophylactic surgery or for those with small and peripherally located tumours, who are eligible for BCS but prefer mastectomy. Currently, there are no universal criteria used for patient selection regarding tumour size and distance from the nipple, but early stage and a size < 3-5 cm in diameter (with no multifocality) and tumour located more than 1-2 cm from the nipple/areolar complex without extensive calcifications have been suggested by different authors (236-238). Jagsi et al. showed that tumour size > 2 cm, tumour margins < 2 mm, premenopausal status and lymphovascular invasion were independent prognostic factors for local tumour recurrence after mastectomy. After 10 years, the local recurrence rate was 1.2% for patients with no risk factors but 10.0%, 17.9% and 40.6% for patients with one, two or three risk factors, respectively. The chest wall was the site of recurrence in 80% of patients. Post-mastectomy RT was an important adjuvant treatment to reduce the local recurrence rates in node-negative patients with such risk factors (239).

1.9.1.2 Breast conserving surgery

In recent years, BCS, when only the tumour and a rim of healthy breast tissue around it are removed, has become the recommended operation for most patients (240). The aim is to preserve function and cosmesis, provided clear margins can be achieved. The choice between BCS and mastectomy depends on the tumour characteristics and the extent of the lesion, defined mainly by preoperative imaging, MG and US as well as patient preferences. Recently, preoperative evaluation with careful surgical planning has added breast MRI as an increasingly valuable adjunct to conventional work-up, as it is essential to avoid residual disease. BCS has the highest success rate in women with DCIS/Tis and T1-2 tumours if there are no other contraindications to adjuvant radiation, but it is not recommended for women at high risk of local tumour recurrence (241). Randomised studies have shown consistently that BCS following supplementary RT for local control provides equivalent survival to mastectomy for the treatment of stage I and II invasive breast cancers. Adjuvant RT following BCS decreases local recurrence rates by approximately 50% and increases breast cancer-specific survival (BCSS) (242-244). This was shown in a meta-analysis of 17 randomised trials including 10,801 patients where adjuvant RT after BCS reduced the tumour recurrence rates from 35.0% to 19.3% and breast cancer-related death rates from 25.2% to 21.4% at 10 and 15 years, respectively (245).

Furthermore, other studies have even reported a survival benefit for patients who receive BCS, and RT compared with those who received mastectomy (246-248). However, a long-term follow-up on ER-positive patients older than 70 years of age with stage I tumours on tamoxifen treatment has shown that there is only a small benefit in local recurrence rate from RT and no improved OS, distant disease-free survival, or breast preservation, concluding that the omission of adjuvant RT is reasonable in such patients (249).

The use of NAC might convert patients with large tumours (> 5 cm) to being candidates for BCS rather than total mastectomy. Similar DFS and OS rates are demonstrated when patients undergo BCS and mastectomy (211, 250). In the setting of BCS and adjuvant RT, it is important to obtain adequate free margins. Adequate margins for invasive carcinomas have been defined as "no tumour on ink" and 2-mm margins for patients with DCIS (251). Re-excision occurs in about 20% of the patients, ranging from 10% to 70% (1-6 cm), but according to Tamburelli et al. in a cross-sectional study, 50% of biopsies subjected to histopathology revealed no residual tumour in re-excised tissue (252). However, the likelihood of finding residual tumour cells was higher if a mastectomy was performed vs a re-excision: 87.3% compared with 37.8%, respectively.

A meta-analysis of 33 studies by Houssami et al. showed that the risk of local recurrence is more than doubled if a free margin of > 2 mm around the tumour is not achieved (253). Another study with 12,656 women also showed

that breast tumour recurrence was higher in patients after repeat surgery, but no difference was seen in the OS regardless of the presence of residual disease (254). However, re-excision is associated with increased risk of complications, costs for health-care service and society because of prolonged hospital stay and increased anxiety levels in patients (255, 256). Re-excision is also often a more challenging surgical procedure because of changes in the initial anatomy and it can lead to a poor aesthetic result (257). Thirty years ago, postoperative adjuvant systemic therapy was not used. This has changed dramatically over the years and is now an essential part of treatment strategies. Repeated studies have proven that successful systemic therapy adds to the improvement of long-term local tumour control (242).

Several studies indicate that BCS has an impact on the patient's quality of life in terms of greater cosmetic satisfaction compared with mastectomy without reconstruction, and similar satisfaction levels compared with mastectomy with immediate reconstruction. The most important factor is the amount of tissue removed (239, 258). To extend the indications for BCS if more tissue must be removed for oncologic safety while expecting the cosmetic result to be poor, several oncoplastic techniques could be adopted to fill in the defect (259).

1.9.1.3 Axillary surgery

In most patients with breast cancers, the axilla is the initial site of metastases, and close to 25% of those with a normal clinical examination will have lymphatic spread (260). Metastasis to the axilla is one of the most important prognostic factors, and axillary surgery is also a staging procedure that determines the need for RT and adjuvant systemic therapy (261, 262).

1.9.1.3.1 Sentinel lymph node biopsy

All patients with newly diagnosed invasive early stage breast cancers who present with a clinically and radiologically negative axilla is recommended axillary staging by sentinel lymph node biopsy (SLNB), which is currently considered the standard of care (263). The sentinel node(s) are the first lymph node(s) draining lymphatic fluid from the breast. The sentinel node can be identified in several ways including using blue dye and/or radioactive tracers or a magnetic tracer technique. A sentinel node can be identified in more than 90% of patients and has low false negative rates at 5-10% (264, 265). After a negative sentinel node biopsy, the risk of an isolated axillary tumour recurrence is < 1%.(266).

1.9.1.3.2 Axillary lymph node dissection

Axillary lymph node dissection (ALND) is a procedure that is associated with potentially significant morbidity and can result in altered sensation, pain and lymphedema in the upper limb (267, 268). ALND usually removes nodes in levels I and II and is now the standard of care in patients with three or more

positive sentinel lymph nodes and when palpable axillary nodes are present intraoperatively (269). Nevertheless, the remaining lymph nodes are negative in 50-60% of patients after completion of ALND (270). This finding resulted in a study, ACOSOG Z0011, where patients with early stage clinically lymph node-negative breast cancer with one or two positive sentinel nodes were randomised to ALND or to no surgery. There were no differences in local recurrence, nodal recurrences (271) or OS between the two groups at a follow-up at almost 10 years after inclusion, which indicated that 85% of all patients with sentinel node could avoid the need for further ALND (272).The ACOSOG Z0011 trial only included patients with tumours up to 5 cm in size who underwent BCS, and thus the results are not applicable to patients undergoing mastectomy, receiving neoadjuvant therapy, or receiving partial breast RT. The SENOMAC trial was designed to investigate the usefulness of ALND vs sentinel node dissection alone also including patients with larger tumours (> 5 cm) eligible for NAC, BCS and mastectomy. Follow-up is by annual clinical examination and mammography for 5 years, and additional controls after 10 and 15 years. Data regarding OS, arm morbidity and health-related quality of life are not yet available (273).

1.9.2 Radiation therapy

In a study of mastectomy tissue specimens in 282 patients with clinical and mammographically unifocal breast cancers, Holland et al. (274) found additional tumour foci within 2 cm of the index tumour in 20% of the patients and > 2 cm from the index cancer in 43%. Thus, the aim of adjuvant RT to the breast is to eliminate residual malignant cells that might remain in the breast even when negative margins are obtained after surgery. Such therapy can be delivered to the breast tumour site in different ways: namely to the whole breast (whole breast radiation), or to a portion of the breast (partial breast radiation) after BCS, to the chest wall after mastectomy, or to the regional lymph nodes. Whole breast radiation after BCS is standard in breast cancer management (242). For BCS, the absolute benefits of RT were greater in patients with unfavorable risk factors, while no benefit was seen in patients with low-risk tumours with no metastatic spread according to Darby et al. in a large meta-analysis of 17 randomised trials (245). The standard dose of radiation after BCS is 50 Gy over 25 fractions, which may or may not involve further (boosting) RT to the tumour bed (275). A hypofractionated schedule, 42.5 Gy over 16 fractions, has been shown to be equally effective as the standard dose in terms of local recurrence risk and cosmetic outcomes, which is an advantage for this option (276).

1.9.3 Chemotherapy

Adjuvant chemotherapy therapy has become a cornerstone of treatment because early breast cancer is a systemic disease. Chemotherapy in various combinations potentially has advantages in terms of better efficacy despite dose reduction, decreased toxicity and a reduced development of drug resistance (277, 278). The combinations that significantly reduce the risk of recurrence are those involving alkylating agents (cyclophosphamide) and antimetabolites (methotrexate and 5-fluorouracil), although the impact on OS is less evident (279). Several trials suggest a benefit in terms of DFS an OS for treatment with anthracyclines or taxanes over other chemotherapies (39).

Chemotherapy is the standard of care for women with node-positive cancers. Those with triple-negative disease, testing negative for oestrogen receptors, progesterone receptors, and excess HER2 protein, benefit more from chemotherapy than those who are hormone receptor positive, but the patient's age and comorbidities also influence the choice of treatment (280). Neoadjuvant chemotherapy is a treatment option in patients with early-stage breast cancers, locally advanced, or inoperable breast cancers to improve operability and provide greater chances for BCS by downstaging the tumour (281, 282). Neoadjuvant chemotherapy can also provide important prognostic information in allowing the evaluation of drug sensitivity during treatment (283, 284). A complete pathological response following neoadjuvant chemotherapy predicts improved DFS and OS, especially among those patients with the highest risk (285, 286). In patients with operable tumours, the long-term outcomes did not differ regardless of whether chemotherapy was administered pre- or postoperatively (287).

1.9.4 Endocrine therapy

Endocrine therapy prevents oestrogen production or blocks its action to minimize stimulation of oestrogen-sensitive tumours. There are various agents available with different treatment mechanisms. The patient's menopausal status is often the primary determinant in the choice of treatment. A meta-analysis of randomised trials evaluating tamoxifen showed that 5 years of treatment halved the recurrence rate during the first 4 years and reduced it by one third in years 5-9 (288). The absolute benefit of tamoxifen was found to be proportional to the risk associated with a given tumour. Breast cancer-specific mortality was also reduced in more than 30% of cases and contralateral cancer was reduced by almost 40% throughout the first 15 years in the group treated with tamoxifen compared with controls (288). However, tamoxifen is also associated with potentially life-threatening side effects such as an increased risk of endometrial cancer and thromboembolic disease (289).

Aromatase inhibitors (anastrozole, exemestane and letrozole) decrease the amount of oestrogen circulating by inhibiting the conversion of androgens to

oestrogen and are used as a treatment of postmenopausal women (290). There are trials that suggest that 5 years of treatment with an aromatase inhibitor is more effective than tamoxifen for the same duration. This has been corroborated by a meta-analysis of close to 32,000 women where the 10-year tumour recurrence risk was 22.7% for tamoxifen and 19.1% for aromatase inhibitors. A strategy equally effective for the reduction of breast cancer mortality is an initial treatment of tamoxifen for 2-3 years followed by aromatase inhibitor therapy for the rest of a 5-year period. This approach is especially appealing for those patients suffering from toxic side effects of either (291). Tamoxifen was also compared with the aromatase inhibitor anastrozole in post-menopausal women in the ATAC trial. This showed prolonged DFS, increased time to tumour recurrence, and decreased distant metastasis and contralateral breast cancers in patients treated with anastrozole. There were also fewer side effects in the anastrozole group compared with tamoxifen (292).

The current recommendation for endocrine treatment is for a duration of 5 years, although the ATLAS trial has proved 10 years of tamoxifen to further reduce the risk of tumour recurrence and mortality after 10 years of treatment (293). Another randomised study, the MA.17 trial, assessed 5 years of extended endocrine treatment with aromatase inhibitor after initial treatment for 4.5 to 6 years apart from a 5-year prior tamoxifen treatment. This regimen resulted in an additional 40% relative risk reduction in breast cancer recurrence (294). After a median follow-up of 6.3 years in 1,918 women extending aromatase inhibitor adjuvant therapy to 10 years compared with controls, there was a 34% reduction in the risk of breast cancer recurrence. No change in OS was noted (295).

1.9.5 Tissue-targeted therapy

The availability of HER2-targeting agents such as the monoclonal antibody trastuzumab (herceptin) has improved the prognosis for patients with tumours showing HER2 overexpression. Trastuzumab's main mechanism of action is antibody-dependent cell-mediated cytotoxicity, cell cycle arrest and some level of apoptosis (45). Data from randomised trials have demonstrated that trastuzumab has a synergistic effect with chemotherapy (296) and significantly improves treatment against HER2-positive breast cancers by decreasing recurrence rates and improving OS and DFS compared with controls, even in patients with metastatic disease (297, 298). Despite this progress, approximately 70% of HER2-positive patients who initially respond to trastuzumab treatment develop resistance within 1 year (299). Cardiotoxicity is a known side effect of trastuzumab treatment. The risk of cardiac dysfunction is about 1% for patients with minimal prior anthracycline exposure but can rise with other combinations of cytotoxic agents (300).

1.10 Prognosis and survival

The TNM stage of breast cancer at the initial diagnosis corresponds well with prognosis and survival. Swedish figures show a nearly 100% 5-year survival rate for women with stage 0 or 1, 80% for stage 2, 60% for stage 3 and 20% for stage 4. The relative 10-year OS among women of all ages has improved over the past 50 years from less than 50% to above 80% (Fig. 6) (16).

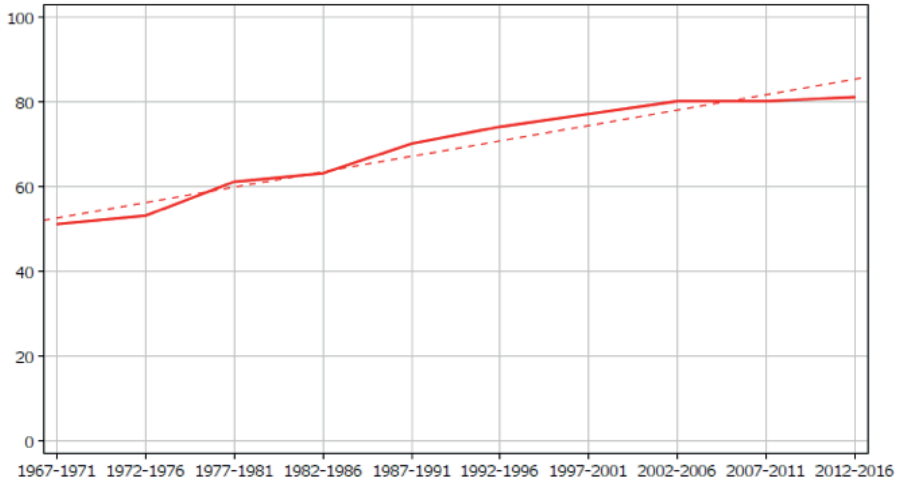

Fig. 6 Relative 10-year breast cancer survival over time (red line). Survival trend (dotted line). NORDCAN©Association of the Nordic Cancer Register

2 AIMS

2.1 Overall aim

The overall aim of this thesis was to assess the value of preoperative breast MRI as a complement to the conventional imaging of breast cancers.

2.2 Specific aims

2.2.1 Paper I

The aim was to evaluate whether incremental findings on preoperative breast MRI influenced the choice of surgical treatment, affected re-excision/reoperation rates, and influenced the decision as when to recommend neoadjuvant treatment.

2.2.2 Paper II

The aim was to evaluate the accuracy of incremental preoperative MRI findings with respect to their concordance with histopathology when used as a complement to conventional imaging modalities.

2.2.3 Paper III

The aim was to evaluate whether the introduction of preoperative breast MRI in the routine management of women with breast cancers influenced the rate of re-excisions, to characterize additional malignant findings in the ipsi- and contralateral breast and to assess type and timing of surgery.

2.2.4 Paper IV

The aim was to report the 10-year follow-up of the POMB study in terms of long-term outcomes of disease-free survival (DFS) and overall survival (OS).

3 MATERIALS AND METHODS

The Papers I, II and IV were prospective randomised multicentre studies, whereas Paper III was a single-centre retrospective cohort study. An overview of the subjects (Papers I-IV) and methods is presented in Table 1.

Table 1. Study designs. KS = Karolinska University Hospital, StG = S:t Goran Hospital, NKBC = National Quality Register for Breast Cancer.

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study design	RCT	Review of results from Paper I	Cohort study	Review of survival data from Paper I
Sample	Women with diagnosed breast cancer included at KS, StG and Vasteras	Women with diagnosed breast cancer included at KS, StG and Vasteras	Women with breast cancer included in Vasteras	Survival data from women with breast cancer included in the POMB study
Data Sources	Medical charts	Medical charts	Medical charts, NKBC	Medical charts
Inclusion period	2007-2011	2007-2011	2016, 2018	2007-2020
Outcome	Incremental MRI findings, altered treatment regimen, re-excision rate	Concordance between incremental MRI findings and histopathology	Re-excision rate, incremental findings, timing of surgery	DFS, OS

3.1 Sample

Women with newly diagnosed invasive and/or non-invasive breast cancers detected by screening or clinical examinations, aged 56 years or younger with supposedly dense breast tissue were included in this Swedish prospective, randomised, multicentre POMB trial. Patients were recruited between December 2007 and March 2011 at Capio S:t Goran's Hospital (Site A), Karolinska University Hospital, Solna (Site B) and Vastmanland County Hospital, Vasteras (Site C). Each site diagnosed and treated 250-500 cases of breast cancer annually. Six hundred and sixty-eight patients were considered eligible. Patients

with contraindications to performing MRI such as medical devices/implants, obesity, inability to lie prone, claustrophobia, mental problems or inability to comprehend the study were excluded. Women with previous breast cancer in the ipsilateral breast, pregnancy/lactation or kidney disease were also excluded from the study population in Papers I, II and IV.

In Paper III, the MRI cohort consisted of women with breast cancers diagnosed by conventional investigations and imaging, who also underwent preoperative breast MRI between January 1 and June 30, 2018. During this period 166 MRI scans were performed for any indication and 123 women underwent breast cancer surgery. The patients in the control group were all women with newly diagnosed breast cancer during the period 1st of January until 30th of June 2016.

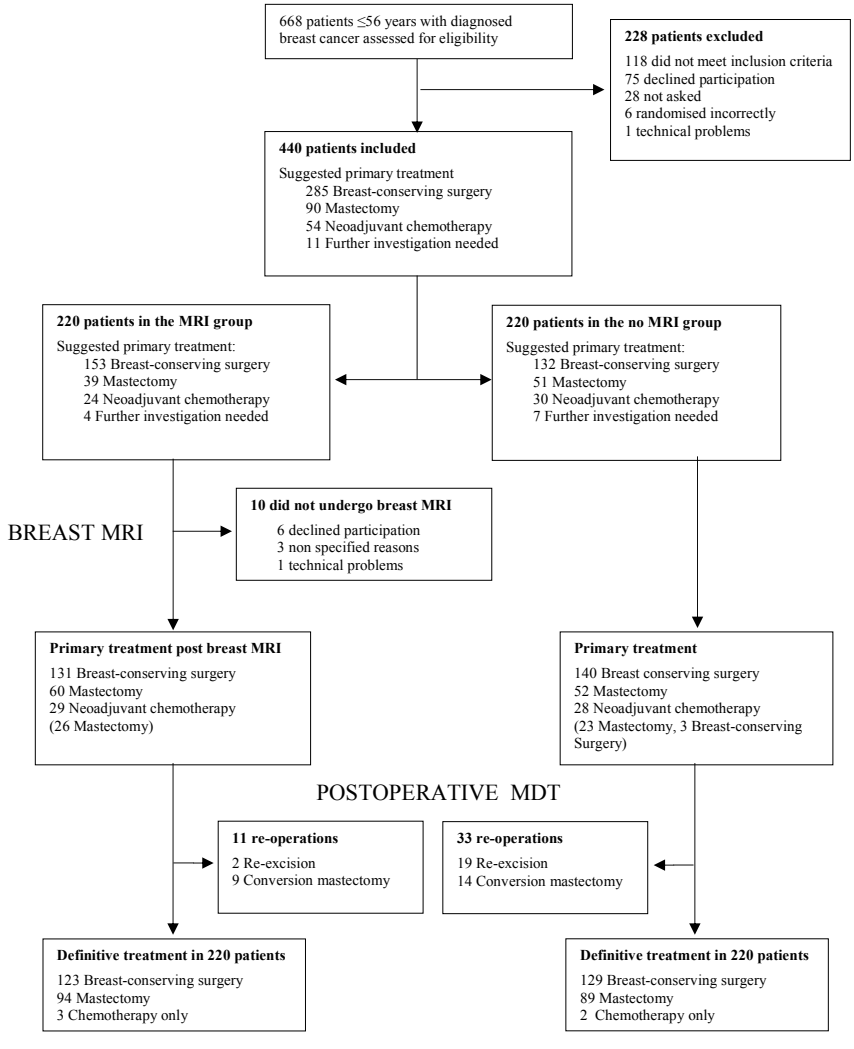

Fig. 7 POMB trial profile.

3.2 Data collection and process

3.2.1 Paper I

When breast cancer diagnosis was confirmed, all eligible patients were invited to participate in the study by the breast surgeon at each site. Using a telephone call to the randomiastion centre (the Regional Oncological Centre in Stockholm), patients were randomised using a computer-generated algorithm and assigned to preoperative breast MRI or no-MRI on a 1:1 basis. Demographics, all prior MG, US, incremental MRI findings (type and number), histopathology data and pre- and postoperative clinical information were collected retrospectively from medical records and entered in Excel files for processing. All patients were discussed at weekly MDT meetings where individual treatment recommendations were confirmed. For patients in the MRI group, the aim was to perform preoperative breast MRI as a complement to ordinary investigation within 2 weeks of breast cancer diagnosis. Incremental MRI findings were discussed at a second pre-treatment MDT meeting, and if necessary, alterations in surgical and/or neoadjuvant treatment were made. All patients' histopathology results were discussed at postoperative MDT meetings regarding tumour margin of the sample, nodal status and molecular markers. In the case of tumour involved margins, re-excision, mastectomy or no measures taken were decided on. Patients with micro or macrometastases not previously detected were recommended axillary lymph node clearance (301, 302). Adjuvant treatment was recommended according to national or regional treatment guidelines (Fig. 7) (16).

3.2.2 Paper II

Data regarding initial MG and US reports from pre-MRI MDT meetings were retrieved retrospectively and compared with adjunctive preoperative breast MRI incremental findings. These were divided into four different categories: larger index tumour (LT) types with a size difference of ≥ 1 cm compared with MG and/or US with impact on treatment approach; multifocal (MF) types regardless of distance between tumours; contralateral (CL) findings; and occult lymph nodes. Information concerning subsequent post-MRI alterations in the treatment plan were noted and collected from MDT records. Because all the pathology sites used synoptic reporting only, original pathology reports were used to evaluate the histopathology of surgical specimens.

When comparing histopathology reports with MG and/or US, a cut-off value of 1 cm was used for a true positive LT. If one or more lesions separated from the index tumour were found malignant at histopathology but undetected by MG and/or US, MF tumours were classified as truly positive. CL incremental tumours were considered as true positives if one or more tumour deposits were confirmed malignant at histopathology in the contralateral breast.

Incremental findings of the lymph nodes were considered true positives if confirmed malignant either in pre-treatment biopsies and/or at final histopathology findings. In the case of more extensive histopathological findings undetected by MRI, these were classified as incremental histopathology findings and thus considered as false negative incremental MRI findings. Decisive incremental findings causing any alteration of the initial treatment plan and total incremental findings were reported for each patient. MRI reports were compared with pre- and/or post-operative histopathology reports in a few cases, when MRI reports were equivocal.

3.2.3 Paper III

Data were collected by retrospective review of patients' medical records including demographic, clinical, radiological, surgical and histopathological results. Patients in the MRI group were referred to preoperative MRI examination according to the breast radiologist. Patients in the control group were assessed according to standard of care alone. Time of management was measured from day of first imaging to surgical treatment. Data concerning re-excisions within 2 months from initial surgery were collected from patient records and the NKBC.

3.2.4 Paper IV

Electronic charts regarding patient demography, clinical data, tumour biology, histopathological tumour characteristics, surgical treatment and neoadjuvant/adjuvant therapy were collected while preparing for Paper I. The data were reviewed and supplemented between March and May 2020. The follow-up interval was calculated as the number of months from the date of randomisation to the date of death, emigration, or the date of the last known follow-up. Patients treated with BCS or mastectomy with chemotherapy were followed up annually for the next 10 years to detect any locoregional and contralateral breast cancer recurrence or distant metastatic disease. Patients who had undergone only mastectomy were examined annually for 5 years. Neo/adjuvant therapies were provided according to the national guidelines based on prognostic markers and stage. All patients aged between 40 and 74 years were followed up thereafter according to the national MG screening program. Patients with locally advanced breast cancers were assessed using conventional chest radiography, computed tomography, or positron emission tomography/computed tomography to evaluate treatment responses. A local tumour recurrence was defined as the reappearance of cancer in the ipsilateral preserved breast or chest wall mastectomy site previously affected by cancer at 3 months after final treatment. They were not distinguished from a theoretically new unrelated cancer. A tumour was denoted as a regional recurrence involving the ipsilateral axilla and/or in the supra/infraclavicular/internal mammary

lymph nodes after adjuvant radiotherapy or 3 months after surgery. Distant metastases were present when metastatic findings were detected by cytological/histopathological or radiological assessments outside regional lymph nodes. CL breast cancers were defined as any diagnosed in the untreated breast during the follow-up and were typically considered to be independent primary tumours.

DFS was defined as the time from randomisation to relapse, or all-cause death, whichever came first. OS was defined as the time from randomisation to death from any cause, or to the date of censoring at the last time the subject was known to be alive. The BCSS was calculated similarly but included only deaths caused by breast cancer.

3.3 Statistical analysis

3.3.1 Paper I

The number of patients needed in the study was estimated to be 440, assuming that 10% of MRI examinations would provide new information leading to a change in management. This power calculation was based on data from a study by Bedrosian et al. where the MRI findings altered the planned surgical management in 26% of 267 patients (185). Descriptive statistics are used to present the main findings of estimated proportions for each randomisation group. Pearson's Chi-squared test was used to test the hypothesis of equal distribution of planned treatments between randomisation groups, and whether there was any difference between the proportion of altered treatments between the two groups. This test was also used to determine whether there was a difference in the proportion of re-excision rates after surgery between the randomised groups. The chances of a breast reoperation and a conversion to mastectomy for a subset of patients initially scheduled for BCS was calculated with the odds ratio (OR) and 95% confidence interval (CI). A P-value < 0.05 was considered statically significant. IBM SPSS Statistics software (v. 20.0; IBM Corp., Armonk, NY, USA) was used to perform all analyses.

3.3.2 Paper II

There were three subsets of patients: (1) those with alteration(s) of treatment plan; (2) those with no alteration of treatment plan; and (3) those with MRI-related conversion from BCS to mastectomy. For each subset, the decisive and total PPV of the incremental findings were calculated with a logistic regression model. A receiver operating characteristic (ROC) curve was constructed for a positive incremental MRI finding (larger tumour or multifocality) through four ratings based on BI-RADS scores. All analyses were performed in Stata version 14 (StataCorp, College Station, TX, USA). Patients with a

reported smaller tumour on MRI compared with conventional imaging, and patients who received neoadjuvant treatment with unconfirmed pre-treatment incremental MRI findings were excluded from statistical analyses.

3.3.3 Paper III

Two-sided t-tests were used to test for significant differences in mean age and body mass index (BMI) between the groups. Fisher's exact test was used to analyse the relationship between the surgical treatment, palpable lesion, metastases, neoadjuvant treatment, re-excision and preoperative MRI. The significance level was set to $P < 0.05$. Data management and analyses were conducted using IBM SPSS Statistics software (version 25.0).

3.3.4 Paper IV

The DFS and OS were estimated and analysed for each group using Kaplan-Meier plots. Log-rank tests were used for comparisons and Cox regression analysis was used to estimate hazard ratios (HRs). Primary analyses were performed according to the intention-to-treat principle, but a per-protocol analysis was also performed. Subgroup analysis of patients with tumour stages I-III was done and $P < 0.05$ was considered statically significant. All statistical analyses were performed using IBM SPSS Statistics software (version 26.0).

3.4 Ethical considerations

The Regional Ethical Review Boards in Stockholm and Uppsala approved studies in Papers I, II and IV (Dnr 2007/1057-31/4, 2008/2020-32, 2009/224-32, and 2020-00351). The Regional Ethical Review Board in the Uppsala and Orebro regions approved the study in paper III (Dnr 2018/260). The researchers involved in the study had no conflicts of interest. The sponsors of the trial financed all breast MRI examinations but had no role in the study design, data collection and analyses, or in the writing of the manuscript. Patient recruitment followed the 55th WMA Declarations of Helsinki-Ethical Principles for Medical Research Involving Human Subjects (2004). Patients were informed about the study and that participation or non-participation would not affect their treatment or care. Written, informed consent was obtained from all participants.

4 RESULTS

4.1 Paper I

A In all, 440 patients were included in the trial: 211 at Site A, 167 at Site B, and 62 at Site C; 220 were randomised to the MRI group and 220 to the control group. According to the intention-to-treat principle (Fig. 7), 10 patients who were randomised to the MRI group but did not undergo the investigation were still included in the MRI group. There was a significantly higher rate of planned BCS randomised to the MRI group compared with the control group. However, the overall distribution of planned treatment and further diagnostic work-up in the two groups did not differ significantly. Demographic and clinical data is shown in Table 2. There were no significant differences in demographic or clinical features between the patients in the two randomised groups.

Table 2. Patient demography, clinical data, tumour characteristics, and treatment of 440 patients included in the POMB study randomised to a preoperative magnetic resonance imaging group or a conventional imaging group.

	MRI (n = 220)			**Control** (n = 220)		
	n	**%**	**median/range**	**n**	**%**	**median/range**
Age at randomization (years)			46/27–55			46/21–56
Menopausal status						
Premenopausal	157	(74.4)		163	(74.1)	
Perimenopausal	28	(13.3)		26	(11.8)	
Postmenopausal	10	(4.7)		17	(7.7)	
Unknown	25	(7.6)		14	(6.4)	
Screen-detected breast cancer						
Yes	83	(37.7)		83	(37.7)	
No	137	(62.3)		137	(62.3)	
Breast density*, dexter						
1	106	(48.2)		103	(46.8)	
2	85	(38.6)		83	(37.7)	
3	24	(10.9)		28	(12.7)	
4	5	(2.3)		5	(2.2)	
Unknown	0	(0.0)		1	(0.6)	

Breast density✣, sinister				
1	104	(47.3)	102	(46.4)
2	85	(38.6)	85	(38.6)
3	26	(11.8)	29	(13.2)
4	5	(2.3)	4	(1.8)
Tumour size				
Tis	19	(8.6)	25	(11.4)
<2 cm	120	(54.5)	129	(58.6)
>2 cm, <5 cm	62	(28.2)	45	(20.5)
>5 cm	19	(8.6)	20	(9.1)
Unknown	0	(0.0)	1	(0.5)
Lymph node metastasis				
0	120	(54.5)	136	(61.8)
1–3	69	(31.4)	65	(29.5)
4–9	15	(6.8)	8	(3.6)
>10	4	(1.8)	4	(1.8)
Unknown	12★	(5.5)	7☆	(3.2)
Type of invasive carcinoma				
Ductal	146	(66.4)	166	(75.5)
Ductal and lobular	6	(2.7)	5	(2.3)
Lobular	15	(6.8)	11	(5.0)
Other	16	(7.3)	10	(4.5)
Type of in situ carcinoma				
DCIS	108	(49.1)	129	(58.6)
DCIS and LCIS	1	(0.5)	5	(2.3)
LCIS	11	(5.0)	6	(2.7)
Other	1	(0.5)	0	(0.0)
ER* status				
Positive	162	(73.6)	158	(71.8)
Negative	37	(16.8)	48	(21.8)
Unknown	21	(9.6)	14	(6.4)
PR* status				
Positive	149	(67.7)	146	(66.4)
Negative	50	(22.7)	59	(26.8)
Unknown	21	(9.1)	15	(6.9)
HER2* status				
Positive	30	(13.6)	32	(14.5)
Negative	168	(76.4)	172	(78.2)
Unknown	22	(10.0)	16	(7.3)

	MRI (n = 220)		**Control** (n = 220)	
	n	**%**	**n**	**%**
Herceptin				
Yes	32	(14.5)	30	(13.6)
No	186	(84.5)	189	(85.9)
Unknown	2	(0.9)	1	(0.5)
Molecular subtype by proxy♣				
Luminal A	62	(28.2)	67	(30.5)
Luminal B HER2-	84	(38.2)	71	(32.3)
Luminal B HER2+	15	(6.8)	15	(6.8)
HER2+	11	(5.0)	17	(7.7)
Triple-negative	24	(10.9)	30	(13.6)
Unknown	24	(10.9)	20	(9.1)
Breast conserving surgery				
Yes	123	(55.9)	129	(58.6)
No	97	(44.1)	91	(41.4)
Radiotherapy				
Yes				
breast	73	(33.2)	78	(35.3)
locoregional	65	(29.5)	60	(27.3)
breast+boost	33	(15.0)	38	(17.3)
locoregional+boost	5	(2.3)	8	(3.6)
No	31	(14.1)	35	(15.9)
Unknown	13	(5.9)	1	(0.5)
Chemotherapy				
Yes	140	(63.6)	137	(62.2)
No	79	(35.9)	82	(37.3)
Unknown	1	(0.5)	1	(0.5)
Endocrine therapy				
Yes	160	(72.7)	153	(69.5)
No	59	(26.8)	66	(30.0)
Unknown	1	(0.5)	1	(0.5)
Chemo- and endocrine therapy				
Yes	104	(47.3)	93	(42.2)
No	115	(52.3)	126	(57.3)
Unknown	1	(0.5)	1	(0.5)

✤Breast density according to American College of Radiology Breast Imaging Reporting and Data System: 1 = 0-25 % breast parenchyma, 2 = 25-50 % breast parenchyma, 3 = 50-75 % breast parenchyma, 4 = 75-100 % breast parenchyma.
★Eight patients had no axillary surgery,☆Four patients had no axillary surgery. *ER = Oestrogen Receptor, PR = Progesterone Receptor, HER2 = Human Epidermal Growth Factor Receptor 2. , ♣Luminal A (oestrogen receptor (ER) positive and/or progesterone receptor (PR)

positive, HER2-; Ki-67 <20%), Luminal B HER2- (ER+ and/or PR+, HER2-; Ki-67 ≥20%), Luminal B HER2+ (ER+ and/or PR+, HER2+; any Ki-67), HER2 enriched (ER- and PR-, HER2+; any Ki-67), Triple-negative (ER-, PR-, HER2-, any Ki-67).

4.1.1 MRI results

Table 3. shows that incremental MRI information was found in 83 of 220 patients (38%) of whom 56 required targeted second-look US of the breast and/or axilla. In 44 patients, the lesions were verified with a biopsy and 21 malignancies were found. Second-look MRI confirmed incremental findings in four patients and three of them were biopsied. Breast density and menopausal status did not differ significantly between the subsets of patients with or without incremental MRI findings. Preoperative breast MRI resulted in no delay of surgery or chemotherapy.

Table 3. Breast MRI—incremental information in 220 randomised patients.

Type of findings in 83 patients	*n*
Multifocal findings	43
Altered tumor size	33
Contralateral findings	24
Suspected pathological lymph nodes	12

4.1.2 Altered treatment

Preoperative breast MRI resulted in altered treatment in 40 of the 220 (18%) patients. There were 22 patients who were converted from BCS to mastectomy and 15 underwent more extensive axillary surgery. There were 24 incremental contralateral findings in these patients, which resulted in four unanticipated contralateral BCS and two mastectomies. In the remaining 43 of 83 patients, MRI findings did not alter the primary treatment plan. Further diagnostic work-up with MG and US or patients' preferences also altered the pre-randomisation planning for both study groups.

The conversion rate from primarily scheduled BCS to mastectomy as the final treatment was significantly higher in the MRI group compared with the control group: 30/153 (20%) vs 13/132 (10%), respectively, (OR 2.3; 95% CI 1.1-4.5; $P = 0.024$; (Appendix 1). One patient originally planned for neoadjuvant chemotherapy received surgery as primary treatment, whereas six

patients not planned for neoadjuvant chemotherapy were allocated to chemotherapy preoperatively.

4.1.3 Reoperation rates

The breast reoperation rate in the MRI group was significantly lower than in the control group: 11/220 (5%) vs 33/220 (15%; $P < 0.001$). The reoperation rates in the subset of patients initially planned for BCS were 8/153 (5%) in the MRI group and 29/132 (22%) in the control group ($P < 0.0001$). The reoperation rate for the axilla did not differ between the groups.

4.1.4 Definitive treatments

Definitive BCS rates were 56% in the MRI group and 59% in the control group. The mastectomy rates were 43% and 41%, respectively. Three patients in the MRI group and two patients in the control group received chemotherapy as the only treatment because of advanced disease (Fig. 7).

4.2 Paper II

The overall MRI sensitivity for identifying the index tumour was 95% (95% CI 91-97% using a cut-off of BI-RADS 4). In a review of data from the original POMB trial (Paper I), MRI revealed incremental findings in seven additional patients. In total, 88 patients had incremental MRI findings and there was alteration of the initial treatment plan in 41. Fig. 8 shows that 99 incremental MRI findings were found in 88 patients (40%) of whom 56 (64%) required targeted second-look US. In 44 patients (50%), the lesions were verified with a biopsy (fine needle aspiration or core) and 21 malignancies were found in 19 patients. Second-look MRI confirmed incremental findings in two patients, and in one the lesion was found to be malignant.

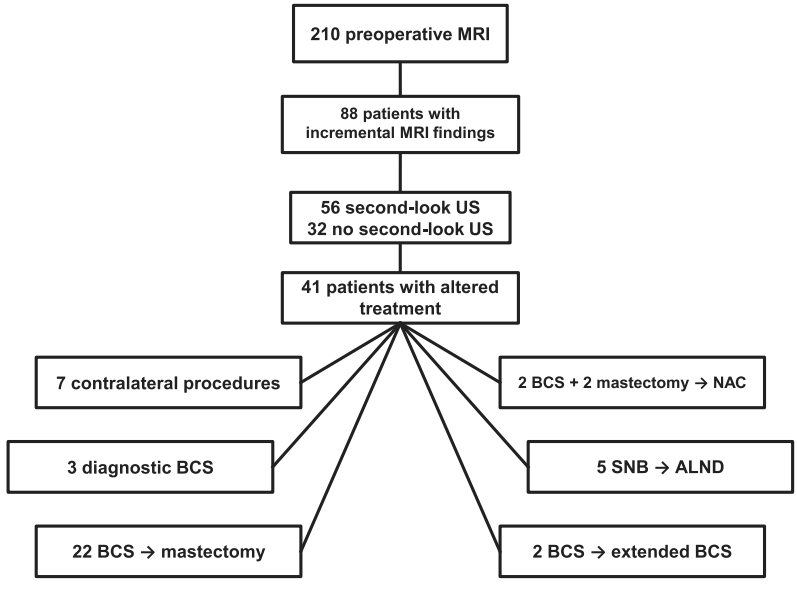

Fig. 8 Flow chart showing the number of incremental diagnostic procedures and distribution of altered management plans among 210 patients who underwent preoperative breast MRI in the POMB trial. MRI = Magnetic resonance imaging, US = Ultrasonography, BCS = Breast-conserving surgery, SLNB = Sentinel lymph node biopsy, NAC = Neoadjuvant chemotherapy.

4.2.1 Incremental findings

In the calculations, 10 patients were excluded, as they received neoadjuvant treatment. Each incremental MRI finding with its corresponding BI-RADS score of 1-5 is reported in Table 4. Preoperative breast MRI findings were false negatives in seven patients when compared with the histopathology findings.

Table 4. Distribution of the incremental MRI findings, their accuracy, in-breast BI-RADS scores and nodes for patients with and without MRI related treatment alterations. LT = Larger tumour, MF = Multifocal, CL = Contralateral. * Smaller tumours not included.

Altered Treatment (n = 39 Patients)									
	BI-RADS								
	5		4		3				
Type of IF	TP	FP	TP	FP	TP	FP	Sum TP	Sum FP	Total
LT	6	3	4	1	0	0	10	4	14
MF	5	1	11	2	1	1	17	4	21
CL	2	0	2	1	0	5	4	6	10
Nodes	–	–	–	–	–	–	9	0	9
Sum	13	4	17	4	1	6	40	14	54
No Altered Treatment (n = 39 Patients)									
	BI-RADS								
	5		4		3				
Type of IF	TP	FP	TP	FP	TP	FP	Sum TP	Sum FP	Total
LT	4	3	0	0	0	1	4	4	8
MF	1	1	4	8	1	5	6	14	20
CL	0	0	0	2	0	12	0	14	14
Nodes	–	–	–	–	–	–	2	1	3
Sum	5	4	4	10	1	18	12	33	45
Total	18	8	21	14	2	24	52	47	99

The PPV values were calculated to assess the accuracy of incremental MRI findings compared with histopathology for three subsets of patients. In those with altered treatment plans because of incremental MRI findings, the association between these findings and histopathology was highly true positive, with a PPV of 74% (95% CI 60-84%). When incremental MRI findings did not result in altered treatment plans, the PPV was 27%: (95% CI 14-44%). The empirical area under the ROC curve (AUC) for larger and/or multifocal incremental in-breast findings based on BI-RADS ratings was 85% (95% CI 78-91%). The associated smoothed ROC curve is presented in Fig. 9.

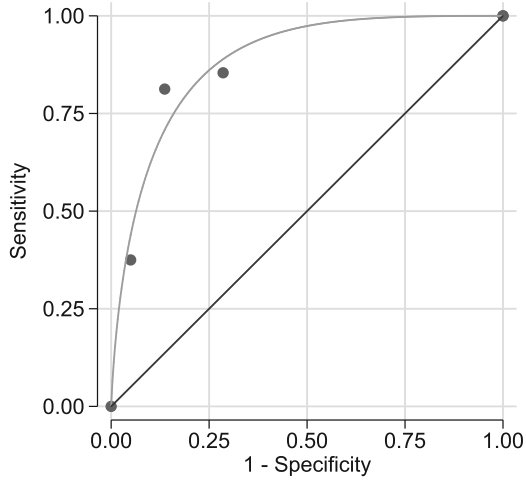

Fig. 9 Receiver Operating Characteristics curve of incremental findings for the MRI group in the POMB trial. Empirical AUC = 85% (95% CI 78-91%).

4.2.2 Altered treatment

Conversion from BCS to mastectomy occurred in 22 patients because of incremental MRI findings (Table 5). The decisive incremental MRI findings were judged as true positives based on histopathology in 20 patients, with a PPV of 91% (95% CI 69-98%). The two other patients, chose conversion to mastectomy themselves. The PPV for the remaining decisive findings associated with MRI-related altered treatment was 83% (95% CI 68-92%). In seven patients, MRI revealed diseases previously not detected by conventional imaging in the contralateral breast. Histopathology confirmed four invasive carcinomas pre- or post-operatively and three diagnostic surgical procedures revealed one radial scar and two benign findings. In seven patients, there were malignant findings only revealed by histopathology. These findings were regarded as false negatives on preoperative breast MRI. Thus, with respect to incremental MRI findings, 115 patients were considered to have true negatives and the negative predictive value (NPV) was 94%, (95% CI 89-97%).

Table 5. Incremental MRI findings and initial tumour sizes in 22 patients with MRI related conversion from BCS to mastectomy, preoperative biopsy results and tumour sizes in final histopathology. MF = Multifocal, LT = Larger tumour, IDC = Invasive ductal carcinoma, ILC = Invasive lobular carcinoma, IPC = Invasive papillary carcinoma, DCIS = Ductal carcinoma in situ.

		Sec. look	Biopsy	Size [mm]					
Age at randomization	Decisive IF	US	result	MG	US	MRI	Histopathology	Confirmed IF	Histopathologic Phenotype
45	MF	No	–	33	17	38 + 22 + 7	75	Yes	ILC
50	LT	No	–	10	0	65	100	Yes	DCIS
50	MF	Yes	Cancer	10	0	14 + 7 + 3 + 20	50	Yes	IDC + DCIS
38	LT	Yes	Cancer	0	5	65	53	Yes	IDC + DCIS
40	MF	Yes	Cancer	15	14	23 + 16	18 + 17	Yes	IDC
41	LT	Yes	Cancer	0	0	51	50	Yes	IDC + DCIS
48	MF	Yes	Atypia	30	21	24 + 13 + 9+6	66	Yes	IDC + DCIS
43	MF	No	–	30	29	32 + 10	32 + 13	Yes	IDC + DCIS
34	LT	Yes	Benign	10	10	43	65	Yes	IDC
45	MF	Yes	Cancer	0	16	17 + 10	15 + 18	Yes	IDC + DCIS
49	LT	Yes	IDC[1]	0	40	78	80	Yes	IPC + DCIS
51	MF	Yes	Cancer	30	18	17 + 8	17+15	Yes	IDC + DCIS
46	MF	Yes	Cancer	15	10	10 + 8	10 + 4 + 4	Yes	IDC + DCIS
46	MF	Yes	Cancer	20	0	23 + 7+5	19 + 8	Yes	IDC + DCIS
54	MF	Yes	IDC + DCIS[2]	12	12	11 + 9	12 + 7	Yes	IDC + DCIS
43	MF	Yes	Cancer	10	7	36 + 6+7	8 + 5 + 8	Yes	IDC + DCIS
48	MF	Yes	Cancer	28	15	17 + 11 + 5 + 5	24 + 10 + 6+10	Yes	IDC + DCIS
47	LT	No	–	0	40	70	70	Yes	IDC + DCIS
54	LT	No	–	18	0	65	90	Yes	IDC + DCIS
50	LT	Yes	DCIS[1]	15	10	27 + 3 foci	30 + 70	Yes	IDC + DCIS
44	MF	Yes	0	0	15	13 + 8+6	15	No	IDC
55	MF	Yes	Benign	15	20	25 + 50	19	No	IDC

[1]Core needle biopsy, [2]MRI guided vacuum biopsy.

4.3 Paper III

One hundred and sixty-six patients had preoperative breast MRI between January 1 and June 20, 2018. Among these, 86 had newly diagnosed breast cancers, but only 84 underwent surgery. During this time, 123 patients were diagnosed with breast cancer. MRI was not performed for 37 patients: three declined, 12 had a contraindication for MRI, 15 had a tumour sized < 10 mm, and in seven patients MRI would not have added more meaningful information.

Ninety-seven patients were diagnosed with breast cancers by clinical examination and conventional imaging (MG and US) and treated with surgery between January 1 and June 30, 2016, for comparison. The groups were not entirely balanced, as the patients subjected to preoperative MRI were slightly younger, leaner and more of them were treated with neoadjuvant chemotherapy.

4.3.1 Re-excision rate

There was one re-excision among 84 patients (1.2%) in the MRI group and three re-excisions in 97 (3.1%) in the no-MRI group. The difference in re-excision rate was not statistically significantly different.

4.3.2 Additional findings in the MRI group

Regarding preoperative MRI, there were additional malignant findings in nine patients, seven in the ipsilateral and two in the contralateral breast (Fig. 10). A subgroup analysis of younger patients (< 59 y) showed that additional findings were more common in the younger study population than in the older, 7/28 vs 2/49. The younger patients were also more often subjected to mastectomy, 16 of 34 vs. 12 of 50 in the older patients, ($P = 0.025$). Seven of 16 patients had additional MRI findings not confirmed malignant on biopsy.

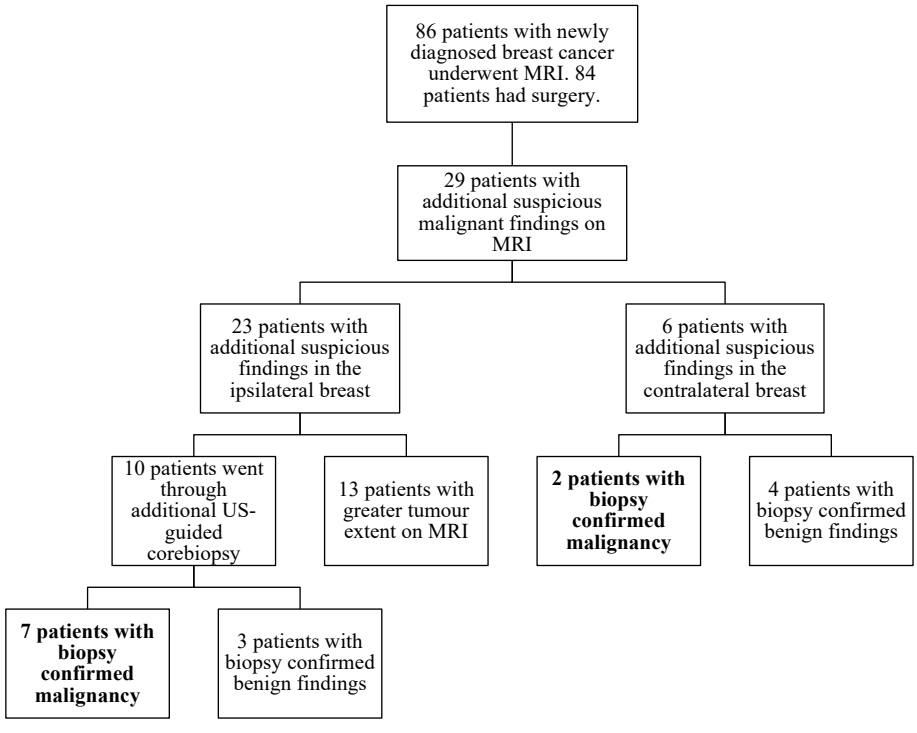

Fig. 10 Additional findings in the MRI group. The boxes in bold show that MRI findings, not previously seen on MG or UL, were malignant in nine patients.

4.3.3 Timing of surgery

Surgery was not delayed because of preoperative breast MRI, as the mean time of management from first imaging to surgery did not differ significantly between the groups, 32.8 and 30.5 days in the MRI group and the no-MRI group, respectively, (ranges 17-84 and 8-71 days; $P = 0.214$). Fifteen patients received neoadjuvant chemotherapy and were not included in this calculation. Nor was there any statistically significant difference in the mean duration of management among patients receiving neoadjuvant chemotherapy, 135.9 days in the MRI group and 138 days in the no-MRI group (ranges 25-181 and 69-176 days, respectively; $P = 0.948$).

4.4 Paper IV

The median follow-up time for OS from randomisation until the end of the study was 10 years. Regarding survival, no patients were lost to follow-up,

but two patients moved away from the study region, and the date of last screening was noted as the end of follow-up for calculating the DFS. There were only minor differences observed between the groups in terms of patient demography and clinical data in the 440 patients included (Table 2). Ten patients did not undergo preoperative MRI as assigned but were included in the MRI group according to the intention-to-treat study plan (191, 303). The DFS was 85.5% in the MRI group and 80.0% in the control group after 10 y ($P = 0.099$; Fig. 11a). The risk of relapse or death was 46% higher in the control group than in the MRI group, (Cox regression analysis; HR 1.46; 95% CI 0.93-2.29). The OS was 90.9% in the MRI group and 88.6% in the control group after 10 y ($P = 0.427$; Fig. 11b). The patients in the control group were at a 27% higher risk of dying than the MRI group (HR 1.27; 95% CI 0.71-2.29). There was a 64% statistically significantly increased risk in the control group of any type of recurrence when combined compared with the MRI group (HR 1.64; 95% CI 1.004-2.670). A per-protocol analysis for DFS and OS was performed excluding the 10 patients who did not undergo MRI and adding them to the controls (HR 1.40; 95% CI 0.89-2.20 and HR 1.16; 95% CI 0.65-2.09, respectively). Seven patients with stage IV disease – not likely to benefit from MRI – were excluded in subgroup analysis. The results indicated that DFS was slightly, but not significantly improved ($P = 0.057$).

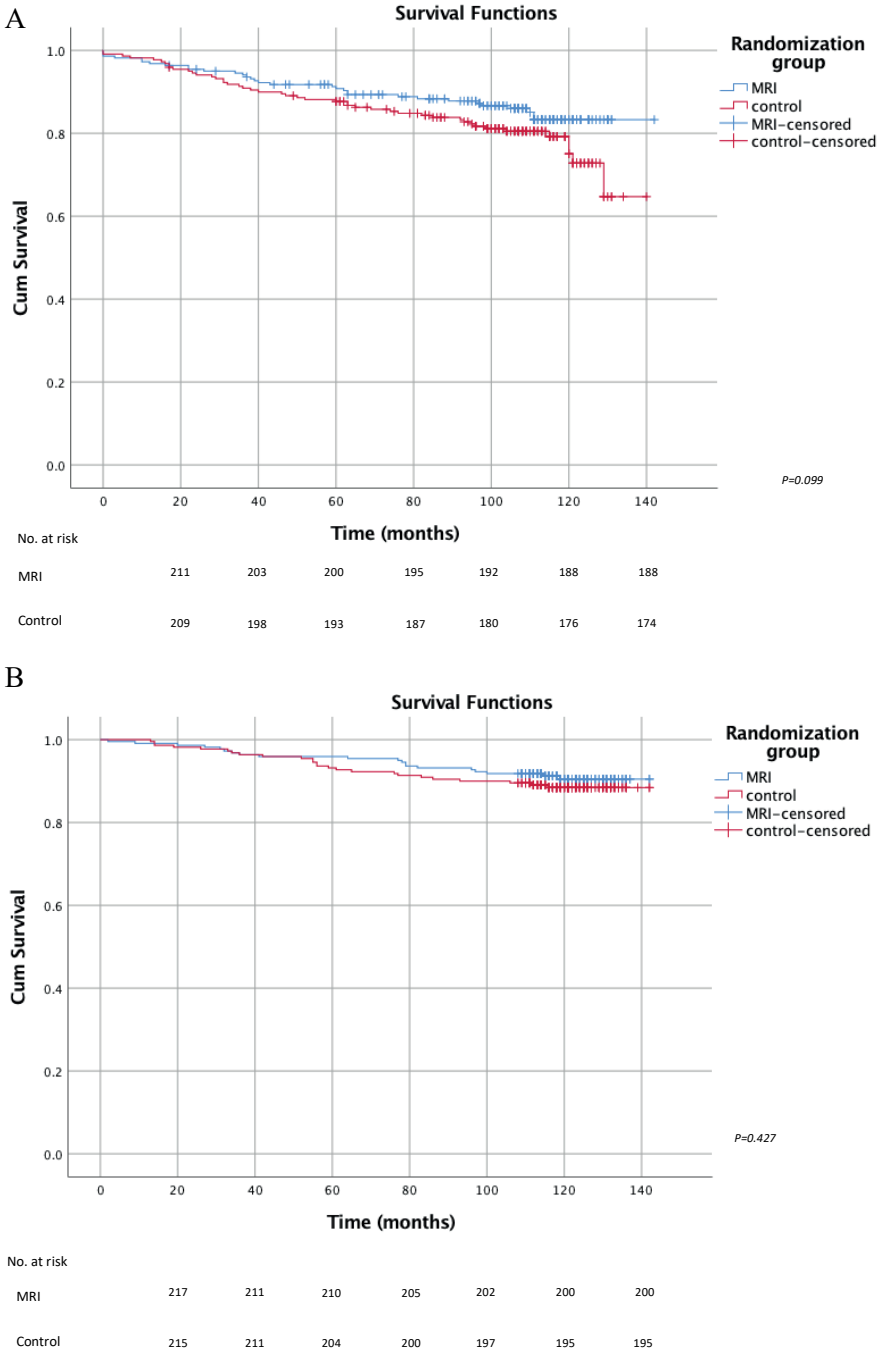

Fig. 11 Kaplan-Meier survival curves during 10 years of follow-up of 440 patients included in the POMB study with newly diagnosed breast cancer who did and did not undergo preoperative magnetic resonance imaging showing (A) breast cancer disease-free survival and (B) overall survival outcomes. Survival curves shown for intention to treat analysis.

5 DISCUSSION

The shift towards BCS in the treatment of women with breast cancers places even greater emphasis on precise preoperative assessment to determine the full extent of the tumour. Inadequate surgical excision varies between centres but is common and is reflected by generally high reoperation rates because of positive surgical margins (304-306). Although effective adjuvant therapies such as RT and chemotherapy in part should manage undetected multifocality and contralateral cancers, these tumours could lead to increased local recurrence rates or new disease (307, 308).

The indications for breast MRI in several different clinical settings continue to be evaluated and reassessed despite of lack of consistent evidence of its short- and long-term outcomes as the use of this rapidly evolving technique is adopted in breast units all over the world. The role of preoperative breast MRI in women with newly diagnosed breast cancer remains controversial regarding surgical outcomes, with diverging results published in different studies. Data on long-term outcomes such as recurrence and survival have not yet been published in any randomised trial.

5.1 Paper I

The POMB trial is the third, randomised, prospective study evaluating breast MRI in the preoperative setting regarding short term clinical outcomes. Data shows that preoperative breast MRI did provide information in addition to conventional imaging (MG and US) in women with newly diagnosed breast cancer. Implementing these results into the multidisciplinary clinical care, the surgical management was altered in 18% of the patients, resulting in a statistically significantly lower reoperation rate and no increased mastectomy rates as final surgical treatment.

Detecting small malignant lesions with MG is often impaired by dense fibroglandular tissue (309). There is evidence indicating that in patients with dense breasts the final surgical outcome will be altered to mastectomy rather than BCS because of occult disease. Thus, women with dense breasts had a 4-fold higher rate of local recurrence compared with women with low-density breasts (310). The selection of a younger study population for the POMB trial was made deliberately to include cases with high breast density where breast MRI is believed to have the greatest impact.

In the randomisation of patients, the number of cases of planned BCS was slightly imbalanced, with a higher number in the MRI group despite the even distribution of baseline characteristics. This higher number in the MRI group increased the risk for reoperation and conversion to mastectomy. Despite this, the breast reoperation rate (re-excision/mastectomy conversion) in this group was significantly lower than in the control group. The final numbers of mastectomies were equal in both study groups, as were the proportions of patients receiving neoadjuvant treatment.

Our POMB trial is thus the first study proving breast MRI to be beneficial in patients with newly diagnosed breast cancers. MRI had no positive impact on the reoperation and mastectomy rates in the two other randomised trials published (192, 193).

The results of the COMICE trial could reflect the large number of centres from which patients were included, along with low-quality MRI techniques and interpretation (192). The contradictory results of the MONET study (using magnetic resonance scanning mammography of nonpalpable breast tumours) could be explained with only one third of the non-palpable BI-RADS grade 3-5 lesions being verified as breast cancers (193).

5.2 Paper II

The POMB trial is the first trial proving preoperative breast MRI to be beneficial for surgical outcomes in terms of a reduction in the reoperation rate and no increased final mastectomy rates in young women with newly diagnosed breast cancers. This is supported by a correct assessment of the incremental MRI findings compared with histopathology and subsequent changes in presurgical planning in most of the patients. In most cases of conversion from BCS to mastectomy, the decisive incremental MRI finding was considered histopathological true positive (PPV of 91%; 95% CI 70-98%). However, the PPV was only 28% (95% CI 15-46%) in the group of patients without altered treatment plans, which also highlights the importance of the MDT approach.

5.3 Paper III

In this retrospective study, preoperative breast MRI as a complement to conventional work-up did not alter the rate of re-excision in patients with newly diagnosed breast cancers. This was despite additional MRI findings that were verified from biopsies as being malignant in 10% of the patients. On the other hand, 7 of 16 biopsy-verified MRI findings proved to be benign, which reflects the negative aspect of MRI with its rather low specificity and the need for further diagnostic work-up.

The re-excision rates in paper III were very low: 1.2% in the MRI group vs 3.1% in the no-MRI group. Similar studies have published rates that vary between 10% and 60% (160, 161). The results of a retrospective study from the US by Patel et al (2015) report that there indeed was a difference in excision rates when comparing preoperative MRI (n = 154) vs no MRI (n = 96) in a group of breast cancer patients. The re-excision rates were statistically significantly lower in patients performing MRI, ($P < 0.001$) (311) but overall were higher than in our study. The randomised POMB study (Paper I) with 440 patients also reported higher re-excision rates that differed significantly between groups: 5% in the MRI group vs 15% in the no-MRI group (191).

Additional MRI findings of malignancies were found in 8% of cases in the ipsilateral breast and 2% in the contralateral breast according to our data, which was like those reported by Killelea et al. where preoperative MRI revealed malignancy in 8% of the patients in the ipsilateral breast (312). In a Finnish randomised study, biopsy-verified malignant findings were found in 12% in the ipsilateral breast (194). Schell et al. found that MRI detected malignant findings in 19% of the patients studied (313).

Additional findings in our study were predominantly detected in patients aged, ≤ 59 y, who also underwent mastectomy more often. This might have been because of the higher sensitivity of MRI in detecting malignant lesions in the dense breast tissue typical of younger women. Similarly, preoperative MRI in the POMB study had an impact on the re-excision rate because of a high number of additional findings in younger patients with breast cancers (191).

In the study by Brück et al., preoperative MRI postponed surgery by a mean of 13 days ($P < 0.001$) (194), whereas in our study the mean number of days from first imaging to surgical treatment only differed by 2 days between the cohorts. This demonstrates that preoperative MRI is well incorporated in the investigation protocols in the Vasteras Breast cancer unit.

5.4 Paper IV

There is controversy over whether detecting additional malignancies using preoperative breast MRI and reducing re-excision rates yields any benefit for survival. The 10-year follow-up of data in the randomised POMB trial addresses this previously unstudied concern. Breast MRI as an adjunct technique to standard preoperative assessment demonstrated a tendency toward improved DFS and OS among women with newly diagnosed breast cancers, especially for patients with stage I–III disease compared with controls, although the difference was not statistically significant.

In our original POMB study, Paper I, preoperative breast MRI was associated with a high number of additional findings such as multifocality and/or contralateral malignancy that would have remained undetected otherwise.

Given such findings, the surgical procedure and adjuvant therapy were adjusted for 20% of patients in the MRI group and the re-excision rate was reduced by one third compared with the control group. Thus, correct primary treatment could be translated into improved long-term outcomes. Whether all MRI-detected additional findings that caused changes in previous treatment plans were indeed biologically relevant remains uncertain (314). Some experts argue that smaller unidentified cancers might not become active or could be treated successfully with RT if not removed surgically (245, 315).

To our knowledge, there are no other similar randomised studies on preoperative breast MRI reporting patient survival data. The existing data comprise small retrospective studies of varying quality, reporting conflicting findings regarding breast cancer recurrence and patient survival rates (186, 316, 317).

5.5 Methodological considerations, strengths and limitations.

Kuhl et al. strongly recommended to biopsy-prove all incremental MRI findings (US/MRI targeted) before significant changes such as con-version from BCS to mastectomy are made (162). This was not per-formed in all cases in our POMB trial, as it would not have had an im-pact on the decision making. Furthermore, MRI-targeted samples are preferable, but only a few patients underwent MRI-guided biopsies because of technical difficulties. Therefore, it is possible that some of the false-positive BI-RADS grade 4 and 5 lesions we found could have been proven benign if MRI-guided biopsy had been available. Additionally, concordance between incremental MRI findings and histopathology could have been improved further if large-format histopathology had been performed. In large-format histopathology, contiguous tissue slices representing the entire cross section of a specimen is examined unlike the traditional small block sampling method. Preserving the inter-relationships of the components of the tumour, and documenting them together in one plane would also have facilitated the detailed radiological–pathological correlation (318).

The optimal time for breast MRI examination during the menstrual cycle is of concern. There could be difficulties in lesion detection and analysis because of prominent background parenchymal enhancement in week 1 and 4 of the menstrual cycle (319). It could also reflect the rather low specificity of breast MRI (160, 161), which exposes the patient to the possible risk of overtreatment with the excision of biologically irrelevant tumour deposits (320). However, our data in the POMB trial showed that incremental breast MRI findings correlated to a high degree with true positive histopathological results with invasive cancers or high-grade DCIS, including findings in the contralateral

breast. This reflects correct management of patients with a higher conversion rate from BCS to mastectomy, resulting in a statistically significantly reduced reoperation rate in the MRI group compared with the controls.

The re-excision rates found in Paper III were very low, 1.2% vs 3.1% in the MRI group and the no-MRI group, respectively. However, these figures are validated by data from the NKBC (Appendix 2). This study was limited because it was a retrospective study with a small sample size and extremely few events. In part, this was because it was based on a well-functioning team and health-care system. There was thus little room for further improvement in terms of further reducing re-excision rates by adding an additional diagnostic modality to the preoperative work-up. Thus, the lack of a significant difference in our study could be an effect of a generally low number of events and cannot rule out a true difference. The demographic data in the groups were also not entirely balanced for younger age and more frequent neoadjuvant chemotherapy in the MRI group compared with the no-MRI group. General guidelines state that MRI should be conducted in women younger than 60 y, because they tend to have denser breast tissue and the more frequent neoadjuvant chemotherapy possibly associated with younger patients. In recent years, neoadjuvant chemotherapy has also increased in clinical use because of supposedly improved OS with the earlier initiation of systemic therapy among high-risk patients.

In our studies, preoperative MRI identified several additional lesions previously not detected by conventional imaging. Nevertheless, no statistically significant improvements in surgical outcome in terms of the re-excision rate were observed in Paper III but were indeed found in Paper I. However, some reports suggest that smaller unidentified cancers might not become biologically active or are successfully treated with RT if not surgically removed (245, 315). Because of the methodological limitations of preoperative MRI (245), it is of major importance to address the absence of long-term data on the effect of preoperative breast MRI in terms of breast cancer recurrence and survival.

Paper IV is a survival analysis based on POMB data with a long follow-up in which no patients were lost to follow-up regarding survival. All MRI studies were evaluated by a few experienced radiologists, being part of the MDT. In this study, younger patients with breast cancer, supposedly those with denser breasts, were included with the aim of studying patients who would benefit the most from preoperative breast MRI. There were differences in DFS and OS between the groups in favour of MRI; however, these did not reach statistical significance. Therefore, our long-time survival results cannot be generalized to all women regardless of age.

Thanks to the excellent prognosis of early-stage breast cancers our results are reasonable, with only a few events occurring even after a long-term follow-up. As nearly 75% of all included patients had ER-positive tumours, one could assume that some events could occur even after a 10-y follow-up. It is known that a small nonsignificant difference in survival between breast

conservative treatment with and without RT translates into a significant difference after a 15-y follow-up (321). Whether this will also occur in our POMB cohort is still unknown, but it indicates the need for a longer follow-up.

6 CLINICAL IMPLICATIONS

According to Swedish national breast cancer treatment guidelines, the use of preoperative breast MRI is recommended in the case of equivocal findings on conventional imaging and in younger patients with dense breasts where MG and US assessments are not optimal. Breast MRI is also recommended as screening for carriers of breast cancer gene mutations (16).

The aim of including younger patients in the POMB trial was to mimic a population with dense breasts with the aim of studying those presumably benefiting the most from MRI. Although this was not possible to realize, as most women in the POMB trial had only low- to moderately dense breasts, the use of preoperative breast MRI for newly diagnosed breast cancers suggests that multifocality and the extent of disease can be assessed more accurately. Additional mammographically and/or US-detected occult lesions in the ipsi- and contralateral breast can also be detected with higher accuracy. In a multidisciplinary setting, this information alters clinical/surgical management strategies by the MDT, contributing to a more optimal treatment for the individual patient, and avoiding non-radical surgery and reoperations without increased final mastectomy rates. The additional procedure of a reoperation causes anxiety for the patient and puts additional strain on available health-care resources that could be avoided. Additionally, the alteration in clinical management leading to a reduced reoperation frequency is supported by a high concordance with histopathological tumour evaluation. Therefore, we can presume that the benefits of preoperative breast MRI as a complement to conventional imaging could potentially reduce local recurrence and improve survival rate.

7 FUTURE PERSPECTIVES

Breast cancer research, diagnostics and treatment have evolved tremendously over the past few decades and will surely continue to do so. There will be substantial changes in imaging technology, less invasive oncoplastic surgery, improved digital pathology, more precise radiotherapy, and tailored systemic adjuvant therapy. Nevertheless, some risks are likely to remain such as the need for reoperation and recurrence of disease, which not only impair cosmesis and functionality but ultimately survival.

The survival benefits of preoperative breast MRI as an adjunct to conventional imaging in patients with newly diagnosed breast cancers have yet to be fully established. There are non-randomised studies addressing this important aspect of preoperative breast MRI, with conflicting results. However, there were no randomised recurrence or survival data prior to our POMB study. In the 10-year follow-up of this study, there were fewer recurrences of all types and improved survival among the patients in the MRI group compared with the controls. The difference in favour of MRI was even more evident in patients with stage I-III tumours, although not enough to establish statistical significance. The excellent survival rates of patients with breast cancer in general with few events and the relatively small sample were probably factors helping to explain why statistical significance was not reached, but these could indicate the need for a longer follow-up to address this issue of great importance. Analogous to our results, in a trial on early breast cancer, local treatments improving local control had little effect on breast cancer mortality during the first few years but had statistically significant effects by 15 y (321).

It is clear that integration of preoperative breast MRI into common practice of breast cancer care results in a high upfront cost and an investment of healthcare resources, namely the increased cost of equipment and examinations. However, with technical advancements, the latest medical equipment has decreased considerably in cost, as has that of MRI scanning. Improved locoregional staging with breast MRI might prove cost effective, as reoperations and new hospitalizations could be avoided. Opponents claim that preoperative breast MRI would increase the lead time to definitive treatment because of the need of additional costly procedures related to the high number of false positive findings. Our data contradict this statement, as no longer lead time to surgical intervention was observed in the MRI group compared with the no-MRI group controls in the POMB trial and confirmed in Paper III. The costs of additional work-up should be evaluated. Unnecessary MRI-related

mastectomies would also increase the cost of care, although the results from our POMB trial do not support this. MRI is already a well-established method at many centres, with several applications in breast imaging. To resolve some of the dilemmas of MRI, for example the limited functional information, and to increase MRI specificity, there are several aspects that have been improved since the initiation of our POMB study and continue to do so. Advances include dedicated multichannel MRI coils, better fatty tissue image suppression, higher-resolution scans and computer-aided detection (CAD) programs. CAD programs enhance the evaluation of neoangiogenesis as a tumour-specific feature using kinetic assessment (322, 323) which is tough, not always accurate when determining the likelihood of malignancy (324, 325). Additionally, the accurate biopsy of lesions and the insertion localization wires under MRI guidance, which were not possible because of limited availability during the greater parts of the POMB study, has improved the value of preoperative staging dramatically (326). These improvements have resulted in higher specificity and thus have given breast MRI a more prominent role in diagnostics.

Short MRI protocols with an average acquisition time of 6 min (327, 328) were investigated for breast cancer screening and diagnosis to lower the costs and to shorten examination times compared with conventional imaging. This would increase availability even to a patient with average risk (329) by diagnosing a breast cancer with high accuracy (330). In a recent study, the mean sensitivity varied from 93% to 96% for each sequence at a mean interpretation time of 44 s (331). However, such shorter MRI still requires refinement because of limited functional information and still yields many false positive findings (327).

MRI at high and ultra-high field strengths, which have become available recently, might also further improve imaging techniques. Ultra-high field MRI at 7 T can provide higher spatial and temporal resolution, improvements in the signal-to-noise ratio and fibroglandular/fat contrast (332, 333). However, such 7 T MRI has its limitations, resulting in reduced image quality in practice. This is one of the main challenges regarding why MRI at ultra-high field strength is not yet being used routinely (334).

The parallel development of new imaging modalities such as breast tomosynthesis can contribute to further improvements in breast cancer diagnostics, new information processing and interpreting. One of the advantages of tomosynthesis is that it reduces the effect of overlapping breast tissue, which is a problem in digital MG, especially in women with dense breasts, potentially leading to false negative or false positive results (335).

In another attempt to improve the detection of breast cancers in women with dense breasts, a cross-sectional study with longitudinal follow-up of 1,516 women was used for breast cancer screening. Abbreviated breast MRI and digital breast tomosynthesis was compared among women with dense breasts showing that abbreviated breast MRI was associated with a significantly higher rate of invasive breast cancer detection (336). In Malmo,

Sweden, tomosynthesis is currently used in a research project but published data are not yet available.

The use of artificial intelligence (AI) and MRI makes it possible to process a vast amount of data with fewer resources than currently, which is especially important because of a general lack of breast radiologists. As imaging technologies and computers have advanced, new potential uses of AI have arisen, potentially helpful to clinicians in terms of assessing individual prognosis and prediction of therapy response. AI might help better estimate tumour volume and thus to describe findings that could be translated into clinical prognostic features.

Furthermore, it is important to evaluate the ultimate quality of life of the patients included in our POMB trial and the effect preoperative breast MRI could have in terms of increased anxiety because of the examination itself and the complementary investigations. However, the existing EQ5D questionnaires have not yet been analysed, but might be included in the analysis of a future study. Despite the distress caused by the procedures, patients could potentially feel reassured because of the extra care and opportunity to have additional dialogue with health-care professionals.

8 CONCLUSIONS

No randomised trial has proven that preoperative breast MRI is beneficial from short- and long-term perspectives. In our prospective randomised POMB trial, preoperative staging with breast MRI in women aged ≥ 56 y was significantly associated with a reduced in-breast reoperation rate and incremental MRI findings showing a high extent of concordance with histopathology. The selection of a younger study population with increased risk for larger, multifocal and contralateral breast cancers in the POMB trial might be the reason for our controversial results. Preoperative breast MRI has been criticized for increasing the mastectomy rate, but the final numbers of mastectomies was not higher among those patients having MRI because of the reduced re-excision rate.

In Paper III, preoperative breast MRI did not affect the rate of re-excision in women with newly diagnosed breast cancers despite additional findings of malignancies. Low re-excision rates in both groups could be a result of adequate and efficient diagnosis and treatment in general but also recommendations of less extensive surgical margins announced in St. Gallen in January, 2013 (251). Additional malignant MRI findings, not detected by conventional imaging, were as expected, mainly detected in younger women because of its higher sensitivity. As a result, those patients were also more often subjected to mastectomy.

In our studies, MRI resulted in no delay of surgery, indicating that preoperative MRI is well incorporated in the investigation process in our breast units. After 10 y of follow-up of patients in the POMB study, preoperative breast MRI as an adjunct to conventional imaging compared with conventional imaging alone resulted in slightly improved DFS and OS. The differences were not statistically significant, at $P < 0.05$. However, P values lie along a continuum of 0 to 1, and so our interpretations also lie along corresponding levels of confidence (337). It could thus be assumed that additional MRI findings must be biologically active to some extent and that adjuvant therapies are not always sufficient to prevent recurrent disease and death. This was especially evident in patients with stage I-III diseases, where MRI potentially can make a difference (8). It is unlikely that the expanding use of preoperative breast MRI will decline, although geographic variability still exists. Increased availability of MRI scanners, technical advancements and higher patient demand are contributing factors to its rising. Our studies suggest that MRI has great value in defining the surgical decision, reducing repeated surgery without too

extensive surgical intervention. A tendency towards positive correlation of preoperative breast MRI use on DFS and OS was observed, although longer follow-up is needed to definitely confirm its association in this group of younger breast cancer patients.

9 SUMMARY IN SWEDISH/ SAMMANFATTNING PÅ SVENSKA

Med trippeldiagnostik (palpation, mammografi och ultraljud samt patologisk undersökning) diagnostiseras de flesta bröstcancrar. De som missas finns ofta hos yngre kvinnor med täta bröst (156). Bröst-MR har visat hög känslighet att påvisa tumörutbredning, multipla cancrar samt inte tidigare känd bröstcancer i det motsatta bröstet hos denna patientkategori. Metoden har ett viktigt användningsområde vid screening av högriskkvinnor (155, 184, 201) men låg specificitet, onödiga mastektomier och kostnader är motargument för denna diagnostiska metod (160, 338). Randomiserade studier har därför efterfrågats.

Det finns endast tre sedan tidigare randomiserade studier som har belyst resultatet av preoperativ bröst-MR vid utredning av bröstcancer. I dessa studier har man dock inte kunnat påvisa några vinster. Den brittiska COMICE studien visade lika många reoperationer i båda grupperna. Flertalet enheter samt radiologer med liten erfarenhet av tolkning och genomförande av MR kan ha påverkat resultatet (192). I den holländska MONET studien som randomiserade kvinnor med icke palpabel misstänkt bröstcancer till preoperativ MR eller ej, sågs paradoxalt nog fler reoperationer i MR gruppen (193). I den tredje, finska studien inkluderades 100 kvinnor med bröstcancer i tidigt stadium. Hälften randomiserades till att genomgå preoperativ bröst-MR eller till kontroller. Hos 20% av patienterna i MR gruppen tillkom fynd som ledde till ändrad handläggning, men dessa hade ingen påverkan på reoperationsfrekvensen. Ingen skillnad i slutlig mastektomifrekvens noterades mellan grupperna (194).

I POMB studien (arbete I), en prospektiv, randomiserad multicenterstudie, undersöktes huruvida utredning med preoperativ bröst-MR skulle påverka valet av primär kirurgisk behandling, minska antalet reoperationer och påverka utformningen av eventuell tilläggsbehandling hos patienter med nydiagnostiserad bröstcancer. Denna studie inkluderade 440 patienter 56 år och yngre med nydiagnostiserad bröstcancer från tre svenska högvolym bröstenheter. Behandlingsplan diskuterades i samtliga fall på multidisciplinär konferens. Totalt randomiserades 220 patienter till preoperativ bröst-MR. Bröst-MR gav ny information hos 38% av patienterna. Dessa fynd ledde till att kirurgisk behandling ändrades hos 18% av patienterna. Bröstreoperationsfrekvensen var statistiskt signifikant lägre i MR-gruppen, 5% jämfört med 15% i kontrollgruppen. Den slutliga andelen mastektomier och andelen patienter som fick

neodajuvant behandling var väsentligen lika i båda grupperna. I arbete II, hos patienter där bröst-MR visat ny information som ledde till ändrad handläggning, stämmer MR överens med PAD i hög grad, PPV 74%: (95%, CI 60-84%). Tjugotvå planerade bröstbevarande ingrepp i MR-gruppen konverterades till mastektomier, varav 20 var sant positiva, PPV 91% (95%, CI 69-98%). Arean under kurvan för alla inkrementella MR fynd i bröst var 85% (95% CI 78-91%).

I arbete III, en retrospektiv studie inkluderades 86 patienter som genomgått preoperativ MR-bröst pga. nydiagnostiserad bröstcancer under perioden januari-juni 2018 i Västerås. Dessa jämfördes med patienter som inte genomgått MR och opererades januari-juni 2016. Data inhämtades från patientjournaler och Nationellt kvalitetsregister för bröstcancer. Reoperations frekvensen i MR gruppen var 1 av 84 (1.2%) och 3 av 97 (3.1%) när ingen MR gjordes. Skillnaden var dock inte statistiskt signifikant. Maligna tilläggsfynd var vanligare hos kvinnor yngre än 59 år och ledde oftare till total borttagning av bröstet. Preoperativ bröst MR ledde inte till förlängd handläggningstid.

Arbete IV, som är en tioårsuppföljning av POMB data (arbete I), visar sig preoperativ bröst MR vara associerad med ökad sjukdomsfri- och total överlevnad, ffa. hos patienter i stadium I-III. Dock var skillnaden inte statistiskt säkerställd.

Sammanfattningsvis ger utredning med preoperativ bröst MR hos patienter med nydiagnostiserad bröstcancer, ny information som leder till ändring i behandlingsplan hos 18%. Reoperationsfrekvensen var statistiskt signifikant lägre i MR-gruppen. Trots en initial ökning av mastektomifrekvens till följd av preoperativ bröst-MR, var antalet slutliga mastektomier lika i båda grupperna. De nytillkomna MR fynden korrelerade väl med histopatologisk undersökning. I arbete III fanns ingen skillnad i reoperationsfrekvens mellan grupperna trots nya maligna tilläggsfynd på MR varav de flesta upptäcktes hos yngre patienter. Tioårsuppföljning av POMB data visar ingen statistiskt säkerställd skillnad i sjukdomsfri- och total överlevnad mellan grupperna.

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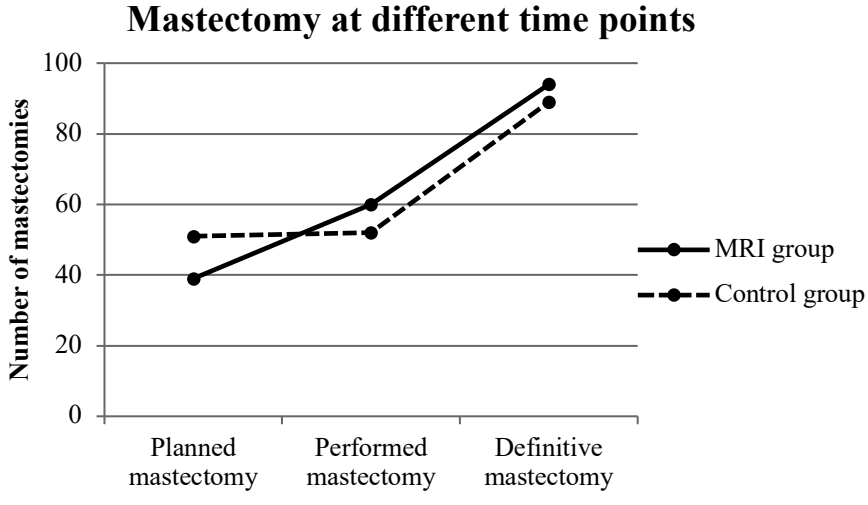
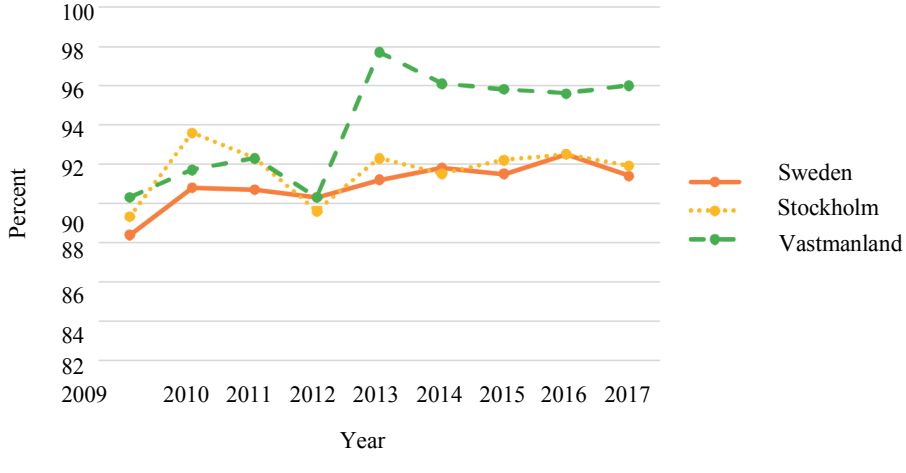
11 APPENDIX



Appendix 1. Mastectomies at different time points.



Appendix 2. Data from NKBC on frequency of a single operation between 2009-2017 in Sweden, Stockholm and Vasteras.

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Preoperative MRI of the Breast (POMB) Influences Primary Treatment in Breast Cancer: A Prospective, Randomized, Multicenter Study

Virginia Gonzalez · Kerstin Sandelin · Anders Karlsson · Wiveca Åberg · Lars Löfgren · Gabriela Iliescu · Staffan Eriksson · Brita Arver

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Abstract
Background Breast magnetic resonance imaging (MRI) has shown high sensitivity in determining tumor extent, multifocality, and occult contralateral breast cancer. Low specificity, unnecessary mastectomies, and costs are arguments against MRI. The purpose of this study was to determine whether preoperative breast MRI would affect primary surgical management, reduce reexcision/reoperation procedures, and influence the choice of neoadjuvant treatment in patients with newly diagnosed breast cancer.
Methods This prospective, randomized, multicenter study included 440 breast cancer patients younger than aged 56 years from three, Swedish, large-volume breast units. Patients were randomly allocated on a 1:1 basis to either preoperative staging with breast MRI ($n = 220$) or no breast MRI ($n = 220$) (control group). Treatment planning of all patients was discussed at multidisciplinary team conferences.
Results In patients randomized to the MRI group, who had an observed higher percentage of planned breast-conserving surgery (BCS) compared with the control group, a change from suggested breast conservation to mastectomy occurred in 23 of 153 (15 %) patients. Breast MRI provided additional information in 83 of 220 (38 %) patients, which caused a change in treatment plan in 40 (18 %). The breast reoperation rate was significantly lower in the MRI group: 11 of 220 (5 %) versus 33 of 220 (15 %) in the control group ($p < 0.001$). The number of mastectomies, axillary reoperations, and the number of patients receiving neoadjuvant chemotherapy after definitive treatment did not differ significantly between the groups.
Conclusions Preoperative staging with breast MRI in women younger than age 56 years altered the treatment plan in 18 % of the patients. Although a higher MRI-related conversion rate from breast conservation to mastectomy was found, the final numbers of mastectomies did not differ between the two groups. The breast reoperation rate in the MRI group was significantly reduced.

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Introduction

Triple assessment, including clinical, radiological (mammography and ultrasonography (US)), and cytological/histological examination is the "gold standard" for the evaluation of breast cancer. After preoperative workup, patients are presented at a multidisciplinary team conference (MDT), where tentative treatment plans are confirmed. Although these diagnostic modalities together will

contribute to accurate staging in the majority of cases, false-negative results occur both in the detection and in the appreciation of the size of the lesion [1]. Conventional imaging modalities have proven inferior to diagnose lobular carcinomas and malignant lesions in dense breast tissue, more frequently found in young women and in women taking hormone replacement therapy [2, 3]. In order to obtain clear surgical margins, tumor mapping is essential, because involved margins may result in reexcision or conversion to mastectomy.

Breast magnetic resonance imaging (MRI) is currently not a standard diagnostic tool in primary breast cancer staging but can serve as a complement in the workup of complex cases with inconclusive mammography and US findings [4]. MRI is a highly sensitive diagnostic method with the ability to detect small tumors in dense breasts. It is considered to be cost-effective as a screening tool in young breast cancer gene mutation carriers [5–7]. MRI is also an adjunct in evaluating neoadjuvant treatment response [8].

Although the use of preoperative breast MRI is increasing, controversy still exists whether preoperative staging with breast MRI improves short-term surgical outcome. A recently published review confers that information gained from routine use of preoperative MRI causes "an unfavorable harm benefit ratio" [9].

The intention of this study was to investigate the value of breast MRI as a complement to triple assessment of breast cancer in young women. We presumed that women with dense breasts would benefit most from breast MRI, although breast density was not an inclusion criterion. Therefore, only women <56 years, most likely to be pre- or perimenopausal, were included.

The purposes of this trial were to evaluate whether breast MRI altered the surgical management, reduced the reexcision/reoperation rates, and if preoperative MRI would influence the decision to recommend neoadjuvant treatment.

Patients and methods

Women younger than age 56 years with newly diagnosed invasive and/or noninvasive breast cancer were included in this prospective, randomized, multicenter trial. Patients were recruited from three Swedish large-volume breast units Capio S:t Görańs Hospital (Site A), Karolinska University Hospital (Site B), and Västmanland County Hospital (Site C). Sites A and B each diagnose and treat close to 500 primary breast cancers annually, whereas site C treats 250 breast cancers yearly. Study inclusion commenced on December 2007 at Sites A and B. Site C started inclusion in February 2009. The last study patient was included in March 2011. A total of 668 patients with both clinical and screen-detected cancers were considered eligible. The age limit was chosen to include women with an increased risk for multifocal and bilateral disease and with dense breast tissue [10]. Breast density according to Wolfe's parenchymal pattern was recorded separately after study closure by one of the authors (GI) [11]. Exclusion criteria were previous malignant disease in the ipsilateral breast, pregnancy/lactation, kidney disease, metal implants, overweight and reduced mobility, claustrophobia, mental illness, and difficulties in comprehension of the study.

Diagnosis was confirmed with fine-needle aspiration cytology or with core-needle biopsy. Nonpalpable tumors were indicated by US-guided tattooing using a carbon suspension or by US-guided needle wire localization. If not visible on US, stereotaxic tumor indication was performed with either carbon technique or hook wires. Subsequently, individual treatment recommendations were confirmed during a weekly MDT. The choice of primary surgical treatment was based on tumor stage, tumor size in relation to the breast size, and biological characteristics of the tumor, as well as patient preferences. Patients with lymph node metastases were eligible for neoadjuvant treatment and participated in neoadjuvant chemotherapy studies. Tumor size was not a prime determinant for neoadjuvant treatment, but tumor size in relation to the breast size was taken into account. Sentinel node biopsy was performed according to national guidelines and axillary lymph node dissection was done in the case of micro and/or macrometastases.

Demographic data and clinical information were collected retrospectively from medical records. Details regarding all image findings (mammography, US, and/or breast MRI), such as presence/absence of multifocality, altered tumor extent, contralateral findings, and pathological lymph nodes, were registered.

Randomization

Eligible patients were asked to participate in the study by the breast surgeon when the cancer diagnosis was confirmed. Written, informed consent was obtained from all participants. Patients entered the trial by means of a telephone call to the randomization center (Regional Oncological Center, Stockholm) made by either the breast nurse specialist or by the surgeon. A computer-generated algorithm was used for randomization and patients were assigned to preoperative breast MRI or no MRI (control group) on a 1:1 basis. The clinical pathway differed somewhat between the units, but in most cases the randomization took place after disclosure of cancer diagnosis and before the pretreatment MDT. A minority of patients were randomized after pretreatment MDT. Subsequently patients' inclusion in the trial was stated in the clinical chart.

MRI procedures

The MRI examinations were performed at Sites A and C. No MRI examinations were performed at Site B. MRI examinations at Site A were performed on a 1.5T MRI system (Signa HDxt®, GE Healthcare). All examinations were performed in the prone position using an 8-channel breast coil. The imaging protocol included a STIR sequence in the axial plane followed by fat-saturated, T1-weighted, contrast-enhanced, dynamic scans (Vibrant® Multi-Phase sequence) in the sagittal plane repeated seven times (including a precontrast sequence) with 90-s time interval. The dynamic sequences were then immediately followed by a fat-saturated, T1-weighted, high-resolution, 3D sequence in the axial plane. Omniscan® (GE Healthcare) gadolinium contrast material was used with 0.2 ml/kg power injected at 3 ml/s. At Site C, the MRI examinations were performed using a 1.5T MRI system (Symphony, Siemens VA30). All examinations were performed in the prone position using a 4-channel breast coil. The precontrast imaging protocol included STIR and T2-weighted sequences in the axial plane and a non-fat-saturated T1-weighted sequence in the coronary plane. The contrast-enhanced, dynamic scans were acquired in the axial plane using a fat-saturated, T1-weighted, multiphase sequence (Vibe®), repeated seven times (including a precontrast sequence) with a 90-s time interval. Dotarem® (Guerbet) gadolinium contrast material was used with 0.2 ml/kg power injected at 2 ml/s. Postprocessing of all contrast-enhanced dynamic scans performed at Site A was performed using a breast MRI computer-aided evaluation software (CADstream, version 4.1 Confirma®). No such aid was used at Site C.

Further diagnostic workup

Patients underwent breast MRI within 2 weeks of randomization at Site A or Site C. If breast MRI findings were consistent with the diagnostic findings before MRI, the initial treatment plan was implemented and the patient was informed of the result by telephone call or letter. Incremental MRI findings, BI-RADS 3 or more were further investigated and included altered tumor extent, multifocality, contralateral lesions, or atypical lymph nodes. Altered tumor extent referred to a larger or smaller tumor detected with MRI compared with mammography/US findings. A size difference more than 1 cm was chosen as a cutoff value. Multifocality was defined as multiple tumors separated from each other, regardless of the distance between each lesion. In the majority of incremental findings, a second-look US examination was performed that targeted the lesion in question and if identified, US-guided tissue sampling was made for confirmation. In October 2009, MRI-guided biopsy was introduced at Site A, but only three patients had this procedure within the study. In a few cases, a second breast-MRI for follow-up was recommended within 3–6 months of primary treatment.

Patients with new information from breast MRI were discussed at a second pretreatment MDT where appropriate amendments were made. Patients allocated to the control group were planned for no further imaging in addition to mammography and US (Fig. 1).

Surgical procedure and specimen handling

The goal was to excise the tumor with macroscopic margins of at least a 10 mm. After BCS tumor specimen X-ray/US was routinely performed. Sentinel node biopsy was sent for frozen-section analysis. The excised tumor was submitted for postoperative histopathological processing.

All patients were discussed during the postoperative MDT. Clear margins were defined as tumor not touching the inked surface for invasive breast carcinomas. In DCIS cases, according to Swedish guidelines, grade and postoperative therapy decided whether margins $\leq$10 mm should be accepted [12]. If equivocal tumor margins, e.g., when the pathologists could not secure clear margins for instance due to fragmented fatty breast tissue, tumor extent and tumor biology was taken into consideration and would impact the decision to reexcise or perform a mastectomy or not to reoperate. Axillary lymph node clearance was recommended to those who had lymph node micro or macrometastases not previously detected [13, 14]. Postoperative adjuvant treatment recommendations followed national or regional treatment guidelines [12, 15].

The Regional Ethical Review Board in Stockholm approved the study, Dnr 2007/4:8, 2008/2020-32, and 2009/224-32.

Statistics

With the assumption that 10 % of MRI examinations would provide new information leading to a change in management, the number of patients needed in the study was estimated to be 440. The power calculation is supported by data from a study that included 267 patients where breast MRI altered planned surgical management in 26 % of patients [16].

The main findings are presented with descriptive statistics of estimated proportion subdivided for randomization groups. Pearson's Chi-square test was used for the following calculations: testing the hypothesis of equal distribution of planned treatment between randomization groups, testing if the proportion of altered clinical treatment differed between the two study groups, and testing if the proportion of reoperations differed after performed surgery between randomization groups. Odds ratio and

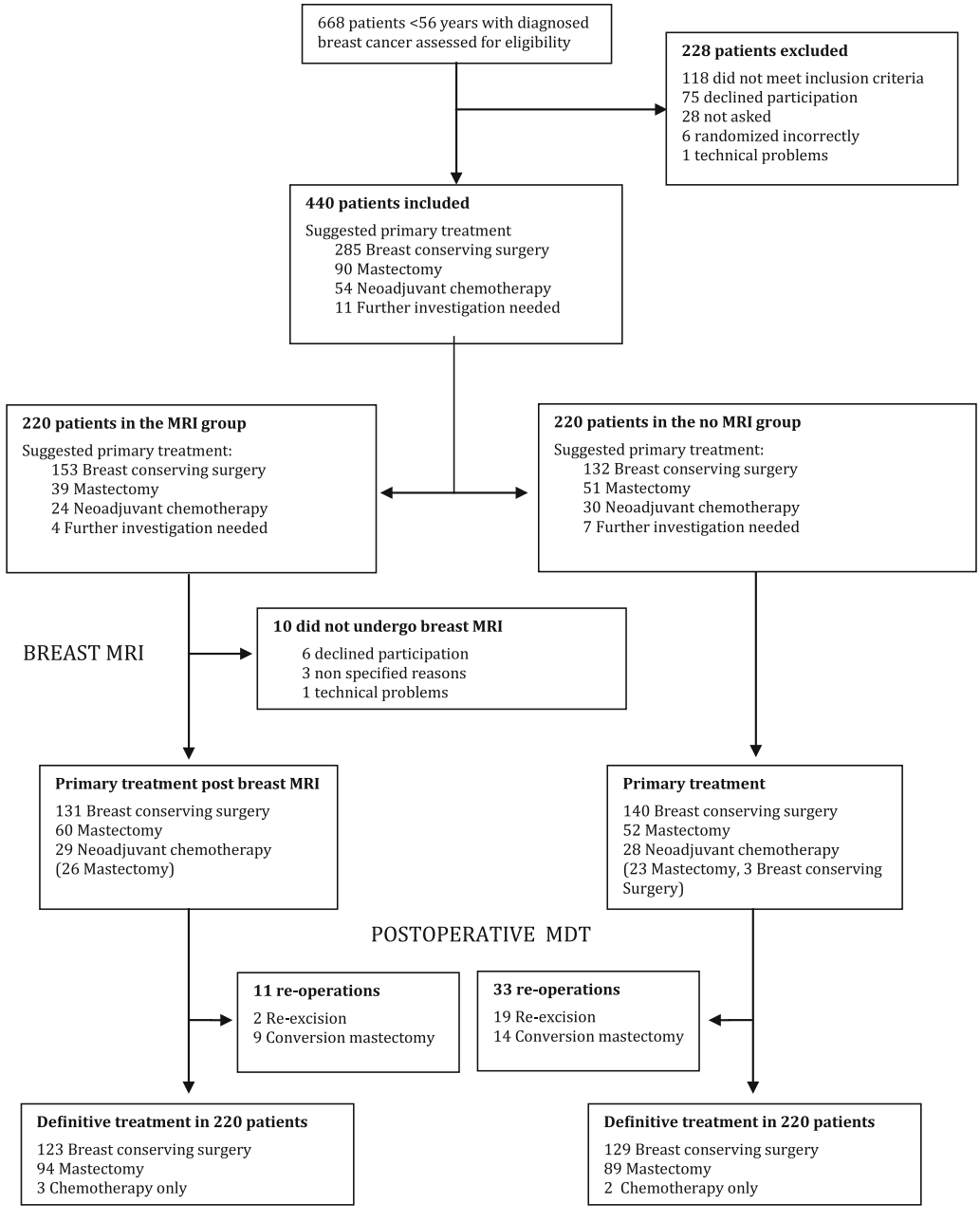

Fig. 1 POMB trial profile

Table 1 Baseline characteristics

	MRI ($n = 220$)			No. MRI ($n = 220$)		
	n	(%)	Median/ range	*n*	(%)	Median/ range
Age at randomization	220		46/ 27–55	220		46/ 21–56
Menopausal status						
Premenopausal	157	(74.4)		163	(74.1)	
Perimenopausal	28	(13.3)		26	(11.8)	
Postmenopausal	10	(4.7)		17	(7.7)	
Unknown	25	(7.6)		14	(6.4)	
Total	220	(100)		220	(100)	
Screen detected breast cancer						
Yes	83	(37.7)		83	(37.7)	
No	137	(62.3)		137	(62.3)	
Total	220	(100)		220	(100)	
Breast density dexter[a]						
1	106	(48.2)		103	(46.8)	
2	85	(38.6)		83	(37.7)	
3	24	(10.9)		28	(12.7)	
4	5	(2.3)		5	(2.2)	
Unknown	0	(0)		1	(0.6)	
Total	220	(100)		220	(100)	
Breast density sinister[a]						
1	104	(47.3)		102	(46.4)	
2	85	(38.6)		85	(38.6)	
3	26	(11.8)		29	(13.2)	
4	5	(2.3)		4	(1.8)	
Total	220	(100)		220	(100)	

[a] Breast density according to Wolfe's parenchymal pattern: 1 = 0–25 % breast parenchyma, 2 = 25–50 % breast parenchyma, 3 = 50–75 % breast parenchyma, 4 = 75–100 % breast parenchyma

95 % intervals were calculated for the chances of a breast reoperation and conversion to mastectomy for a subset of patients initially scheduled for breast-conserving surgery. A p value <0.05 was considered statically significant. Analysis was not adjusted for surgical method. All analyses were performed with IBM SPSS Statistics version 20.

Role of the funding sources

The sponsors of the trial financed all breast MRI examinations but had no role in the study design, data collection, data analyses, or in the writing of the manuscript.

Results

A total of 440 women entered the trial: 211 at Site A, 167 at Site B, and 62 patients at Site C. Two hundred twenty patients were randomized to the breast MRI group and 220 to the control group. Ten subjects randomized to MRI never underwent this study but were included in the MRI group according to the intention-to-treat principle (Fig. 1). Baseline characteristics are shown in Table 1.

Table 2 Breast MRI—additional findings in 220 randomized patients

Type of findings in 83 patients	*n*
Multifocal findings	43
Altered tumor size	33
Contralateral findings	24
Suspected pathological lymph nodes	12

Pre-randomization treatment planning

Patients randomized to the MRI group had a significantly higher rate of planned BCS (153/220, 70 %) compared with the control group (132/220, 60 %). However, the overall distribution of planned treatment (type of surgery/ neoadjuvant chemotherapy) and further diagnostic workup in the two groups before randomization did not differ significantly.

MRI results

In 83 of 220 patients (38 %), breast MRI revealed incremental information. The additional findings are listed in Table 2. As a consequence, 56 patients underwent targeted second-look US. In 44 patients, the lesions were detected and a biopsy performed. Four patients required second-look MRI and three were biopsied. Eleven patients with MRI-detected lesions repeated MRI after 3–6 months. No further investigations were required nor changes in treatment plans occurred for the remaining 12 patients. There was no significant difference in menopausal status or breast density between the subsets of patients with or without incremental MRI findings. Time from diagnosis to primary treatment was equal in both groups; thus MRI did not prolong waiting time.

Altered treatment

In the MRI group, patients primarily scheduled for BCS showed a significantly higher rate of conversion to mastectomy as final treatment; 30 of 153 (20 %) compared with 13 of 132 (10 %) in the control group (odds ratio = 2.3; 95 % confidence interval [CI] 1.1–4.5; $p = 0.024$; Appendix). Six patients not originally planned for neoadjuvant chemotherapy were allocated to chemotherapy preoperatively, whereas one patient planned for neoadjuvant chemotherapy received surgery as primary treatment (Table 3).

Table 3 Altered treatment post MRI/no MRI in 440 patients

				Suggested treatment before ± MRI						
		Total	BCS	BCS + SLNB	BCS + ALND	Mastectomy + SLNB	Mastectomy + ALND	Neoadjuvant chemotherapy	Further investigation	2BCS + SLNB
Primary treatment MR	BCS	**9**	9	0	0	0	0	0	0	0
	BCS + SLNB	**87**	2	85	0	0	0	0	0	0
	BCS + ALND	**31**	0	25	4	2	0	0	0	0
	Mastectomy + SLNB	**29**	1	10	0	15	0	1	2	0
	Mastectomy + ALND	**31**	0	10	2	7	12	0	0	0
	Neoadjuvant chemotherapy	**29**	0	2	0	2	0	23	2	0
	2BCS + SLNB	**4**	0	2	1	0	1	0	0	0
	Total	**220**	**12**	**134**	**7**	**26**	**13**	**24**	**4**	**0**
Primary treatment no MRI	BCS	**7**	7	0	0	0	0	0	0	0
	BCS + SLNB	**98**	0	93	0	2	0	0	3	0
	BCS + ALND	**33**	0	23	7	1	0	2	0	0
	Mastectomy + SLNB	**28**	0	1	0	24	1	0	2	0
	Mastectomy + ALND	**24**	0	0	0	10	13	0	1	0
	Neoadjuvant chemotherapy	**28**	0	0	0	0	0	28	0	0
	2BCS + SLNB	**2**	0	0	0	0	0	0	1	1
	Total	**220**	**7**	**117**	**7**	**37**	**14**	**30**	**7**	**1**

BCS breast-conserving surgery, *2BCS + SLNB* two excisions in index breast during same operation+SLNB, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

Table 4 Altered treatment due to breast MRI findings in 40 women out of 220 patients randomized to MRI

Primary treatment	Suggested treatment before MRI							
	Total	BCS	BCS + SLNB	BCS + ALND	Mastectomy + SLNB	Mastectomy + ALND	Neoadjuvant chemotherapy	Further investigation
BCS + SLNB	**2**	1	1[b]	0	0	0	0	0
BCS + ALND	**4**	0	3	0	1	0	0	0
Mastectomy + SLNB	**12**	1	10	0	0	0	1	0
Mastectom + ALND	**13**	0	9	2	2	0	0	0
Neoadjuvant chemotherapy	**5**	0	1	0	2	0	1[b]	1
2BCS[a] + SLNB	**4**	0	2	1	0	1	0	0
Total	**40**	**2**	**26**	**3**	**5**	**1**	**2**	**1**

[a] Two excisions in index breast during same operation

[b] Altered treatment in the contralateral breast

Altered treatment due to MRI findings occurred in 40 of 220 (18 %) patients (Table 4). Twenty-two patients converted from BCS to mastectomy and 15 patients underwent axillary clearance instead of sentinel node biopsy. One of these converted from mastectomy to BCS. As a consequence of MRI findings, three patients received neoadjuvant chemotherapy instead of surgery as primary treatment and one patient received a mastectomy instead of neoadjuvant chemotherapy. Contralateral findings were described in 24 of 220 patients, which resulted in four unanticipated contralateral BCS and two mastectomies. In the remaining 43 of 83 patients, MRI findings did not alter the primary treatment plan. For both study groups, altered pre-randomization planning also could be due to results of further diagnostic workup with mammography and UL or patients' preferences (Table 3).

Reoperation rates

The overall breast reoperation rate in the MRI group was significantly lower than in the control group ($p < 0.001$). The ipsilateral breast reoperation rate was 11 of 220 (5 %) and 33 of 220 (15 %) respectively in the two groups. One patient in the MRI group underwent reexcision in the contralateral breast, which is not included in the calculation. Two patients in the control group were reoperated twice in the ipsilateral breast, and one of these patients also needed a repeated procedure in the contralateral breast. No significant difference in axillary reoperation rates between the groups was found.

Reoperation rates after BCS

The reoperation rates in the subset of patients initially planned for BCS were 8 of 153 (5 %) in the MRI group and 29 of 132 (22 %) in the control group ($p < 0.0001$).

Definitive treatment

BCS rates were 123 of 220 (56 %) in the MRI group and 129 of 220 (59 %) in the control group, and the mastectomy rates were 43 and 41 % respectively. Of those 29 and 28 patients in each group receiving neoadjuvant chemotherapy, 3 and 2 patients respectively with metastatic disease never had surgery (Fig. 1).

Discussion

In this study, preoperative breast MRI did provide additional information: both in the ipsi- and the contralateral breast and in the axilla that altered the surgical management in 18 %. An increased number of patients planned for

BCS received mastectomy after MRI and fewer reoperations occurred in this group. Neoadjuvant chemotherapy rates were similar in both groups. Until now, only two randomized studies have assessed the efficacy of breast MRI regarding the surgical outcome in women with newly diagnosed breast cancer [17, 18]. Both trials failed to show any additional benefit of breast MRI to standard assessment.

This trial is the third randomized, prospective study. It specifically selected young women with symptomatic and screen-detected breast cancer, younger than age 56 years, where breast MRI is supposed to have the greatest impact. Because it is difficult to ascertain the influence of sex hormones on breast density on an individual level, pre- as well as perimenopausal women were included. The number of planned BCS was higher in the MRI group than in the control group: 153 versus 132. Because both groups were evenly distributed concerning age, menopausal status, screen detected cancer, breast density, and mammographic tumor extent the main reason for the unbalance is assumed to be related to chance. Tumor size in relation to breast volume was not analyzed. At pretreatment MDT, most patients' participation in preoperative MRI of the breast (POMB) was known, but the allocated treatment arm was unknown in the vast majority of cases. It could not be ruled out that the unblinded randomization design could have influenced the unbalanced planned treatment. The higher number of planned BCS in the MRI group per se, increased the risk for reoperation in the MRI group, but the breast reoperation (reexcision/mastectomy conversion) rate in this group was found to be significantly lower than in the control group. The final numbers of mastectomies were equal in both study groups as was the proportion of patients receiving neoadjuvant treatment.

The results presented in our study are contradictory to prior randomized studies. The COMICE trial included women with biopsy verified breast cancer; all planned for BCS with reexcision rates as study endpoint. Reoperation rates were not significantly lower in the MRI group. The authors of the COMICE trial pointed to limitations in their study, e.g., its inclusion of patients from a number of small centers where technical factors and varying degree of experience among involved radiologists could have influenced the MRI results [17].

In the MONET trial, the second, randomized, controlled trial, only patients with nonpalpable BI-RADS 3-5 lesions were included and randomized to MRI or to no MRI in addition to standard assessment. The MONET trial assessed the reexcision rates after primary surgery. The number of reexcisions in that study was paradoxically higher in the MRI group compared with the control group. The number of mastectomies did not differ between the groups. The MONET trial could be questioned for being underpowered, as only one third of the included patients had confirmed malignant lesions, whereas in the POMB study all randomized patients had a verified cancer diagnosis.

A limitation of the present study is that not all MRI-detected lesions were biopsy-proven, which is strongly favored by Kuhl et al. [19]. The reason is that the result of the biopsy would not have changed the type of surgery performed in these cases. US-guided tissue sampling was used in two thirds of the patients with new information from MRI when the result could influence further treatment. Only a few patients underwent MRI-guided biopsies, because the method was available only during the late part of the study. The additional MRI information led to a reduction of planned BCS and increased the number of mastectomies, which in turn reduced the reoperation rate.

A meta-analysis of nonrandomized studies assessing the impact of preoperative breast MRI on surgical management by Houssami et al. implies that more extensive, unnecessary surgery is performed in patients due to MRI, thus corroborating the COMICE but not the MONET trial [9]. Our data support that preoperative breast MRI as an adjunctive image modality affects the clinical management in women with breast cancer who are younger than age 56 years. The additional information gained from preoperative MRI in relation to histopathological results, disease-free survival, and health-related economic consequences will be addressed in future studies.

Conclusions

Although a higher MRI-related conversion rate from breast-conserving surgery to mastectomy was found, the final numbers of mastectomies did not differ between the two groups. Furthermore, preoperative staging with breast MRI was significantly associated with a reduced in-breast reoperation rate.

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Conflict of interest The authors declare no conflict of interest.

Appendix

See Fig. 2.

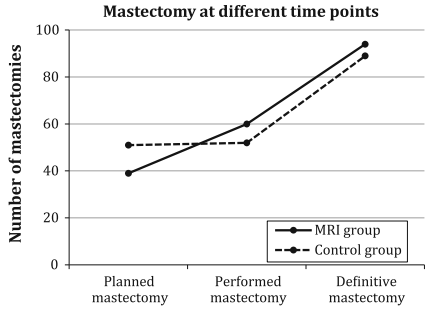

Fig. 2 Mastectomy at different time points

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Paper II

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Research article

The accuracy of incremental pre-operative breast MRI findings – Concordance with histopathology in the Swedish randomized multicenter POMB trial☆

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ABSTRACT

Purpose: The Pre-Operative MRI of the Breast (POMB) trial was a randomized, prospective, multicenter trial evaluating the impact of pre-operative breast MRI on treatment regimens and short-term surgical outcomes in women up to 56 years of age with breast cancer. The purpose of this study was to evaluate the performance of pre-operative breast MRI in the POMB trial with respect to incremental MRI findings - over conventional breast imaging methods – and their concordance with histopathology.

Patients and methods: Two-hundred and ten patients (n = 210) participating in the POMB trial underwent pre-operative breast MRI at two Swedish breast units.

Positive predictive values (*PPV*) for the incremental MRI findings were calculated for three subgroups of patients with: 1. alteration/alterations of treatment plan; 2. no alteration of treatment plan; and, 3. MRI-related conversion from BCS to mastectomy.

Area under the receiver operating characteristic curve (AUC) was calculated using in-breast BI-RADS based ratings for the whole MRI group.

Results: After exclusions a total number of 99 incremental findings in 78 patients were eligible for statistical analysis resulting in a *PPV* = 74%: (95% CI 60–84%) in 39 patients with MRI related alterations of initial treatment plans and 27%: (95% CI 14–44%) in 39 patients without.

Positive predictive values of incremental findings decisive for specific treatment alteration/s were 83% (95% CI 68–92%) in patients with any alteration of initial treatment plans and 91% (95% CI 70–98%) for patients (n = 20/22) with conversion from breast conserving surgery to mastectomy.

The empirical AUC for the incremental findings in the whole MRI group was 85% (95% CI 78–91%).

Conclusion: Breast MRI, performed and evaluated together with conventional breast imaging methods can provide relevant information at a high degree of accuracy in the pre-operative setting.

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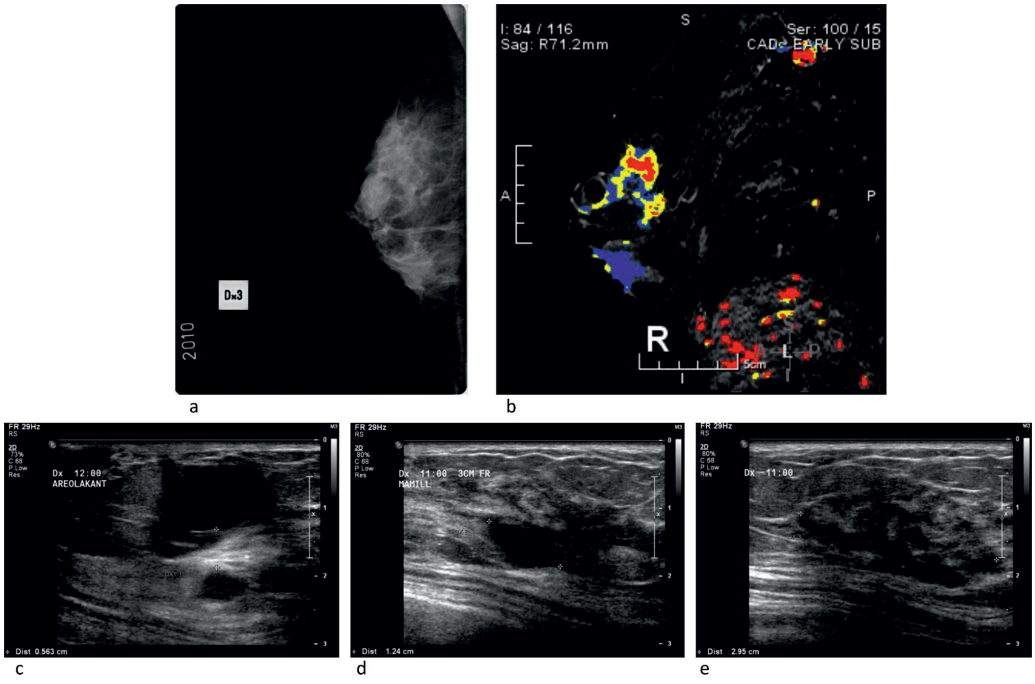

Fig. 1. Forty-one year old patient with a 25 mm large, palpable lump in the upper part of the right (Dx) breast. Initial mammography (a) and ultrasound (not shown) revealed a 23 x 12 mm cyst corresponding to the palpable finding. Cytology from the cyst fluid yielded cancer cells and the patient was randomized to perform pre-operative breast MRI (b) showing malignant contrast enhancement within a tumor area measuring 50 mm. Second-look ultrasound (c–e) found a refilled cyst along with three areas of low echogenicity measuring 8, 12 and 30 mm, where core needle biopsy revealed invasive cancer. Final histopathology resulted in 40 mm invasive ductal carcinoma grade III with surrounding DCIS grade III within a total area of 50 mm.

1. Introduction

Magnetic resonance imaging (MRI) of the breast is an important diagnostic tool [1,2]in several clinical situations [3,4], e.g. diagnostic uncertainties after conventional imaging, screening among gene mutation carriers, and assessment of residual and/or recurrent disease.

Although breast MRI is the most sensitive imaging test [5–7], for determination of disease extent in the ipsilateral and contralateral breast, the method is still under debate [8], in the pre-operative setting.

However, pre-operative MRI has been shown to be of value in subgroups of patients with lobular cancer [9,10] and current guidelines [3,4] recommends staging with MRI in this setting.

Several studies [11–16] with various designs have assessed short-term outcomes and impact on therapeutic approaches of preoperative MRI, both among patients eligible for breast conserving surgery and patients in broader clinical settings.

To our knowledge, no accuracy data of incremental MRI findings has previously been reported from a randomized controlled study performed in a general preoperative setting.

The purpose of this study was to evaluate the performance of pre-operative breast MRI in the POMB [17] trial with respect to incremental MRI findings - over conventional breast imaging methods - and their concordance with histopathology.

2. Patients and methods

2.1. Patient population

Both patients and MRI method are described in the POMB trial. [17] In summary, 440 patients up to 56 years of age with newly detected breast cancer, scheduled for BCS, mastectomy or neoadjuvant treatment were randomized to either preoperative MRI (n = 220) or to controls (n = 220) without MRI. After exclusion, 210 patients had pre-operative breast MRI. The study was approved by the ethics committee [17].

MG and breast US as well as second-look US were read in a routine clinical setting by experienced breast-radiologists at the center of patient inclusion. The MRI exams were performed and read at two of the three centers of patient inclusion. At site one, read and double read by two experienced readers and at site two, by one single experienced reader.

All index tumors were biopsy verified either with stereotactic vacuum biopsies and/or US guided FNA and/or core needle biopsy prior to the MRI examinations.

For this work, records from multidisciplinary team conferences (MDT) and MRI reports were, reviewed for incremental MRI findings over initial mammography (MG) and ultrasound (US).

2.2. Evaluation criteria

Incremental findings (IF) diagnosed on MRI were divided into four categories: 1. Larger index tumor (LT) with impact on treatment approach; 2. Multifocality (MF); 3. Contralateral (CL); and, 4. Occult

lymph node.

In order to adjust for the radiological uncertainty in assessment of tumor sizes [18] a larger index tumor was described when a size difference of ≥ 1 cm compared to MG and/or US was reported. Multifocality was described as more than one tumor in the affected breast, regardless of the distance between the individual lesions. MRI findings of a smaller index tumor, ≤ 1 cm compared to MG and/or US were classified as new MRI-related information.

The MRI detected lesions were assessed according to the BI-RADS MRI classification system [19].

When one or more IF was considered significant enough to cause alteration/s of the initial treatment plan/s, a recommendations for further work-up was taken at the MDT. For the majority of these cases, a second-look US examination was targeted at the lesion and if identified, an US-guided fine needle aspiration and/or core needle biopsy was performed. Treatment changes effectuated without pre-treatment confirmation of malignancy were due to recommendations from MDTs.

An example of a larger tumor confirmed with second-look US and core needle biopsy is presented in Fig. 1. MRI-guided biopsy was only available in the late part of the POMB trial and only four such procedures were undertaken. To minimize delay, the timing of the MRI examination in relation to menstrual cycle was not taken into consideration.

2.3. Preparation and fixation of histopathological specimens

The surgical specimens were fixated in 4% buffered formalin and then paraffin embedded. Thereafter, the samples were sliced at 4 μm and either whole mounted or cut into smaller segments. All pathology sites used synoptic reporting and only original pathology reports were used for the study.

2.4. Accuracy classification of the incremental findings

A larger extension of the index tumor was classified as true positive if the corresponding histopathological tumor size exceeded the selected cut-off of ≥ 1 cm compared with MG and US results. Multifocality per se was classified as true positive if one or more lesion/s separated from the index tumor were found malignant at histopathology.

A contralateral IF was considered true positive if one or more tumor deposits were confirmed malignant at histopathology. Incremental findings of lymph node/s were considered true positive if confirmed malignant either in pre-treatment biopsies and/or at final histopathology after axillary surgery.

A histopathological finding of more extensive tumor undetected by MRI was classified as a histopathological incremental finding and considered a false negative "IF".

The accuracy was assessed for the total number of IFs in each patient, with and without related treatment changes performed. Since more than one IF could be found in a single patient with MRI related alterations of initial treatment plan, the accuracy of the decisive IF causing that specific change of treatment was also assessed.

2.5. Statistical analysis

Positive predictive values (*PPV*) for total and decisive IFs were calculated for three subsets of patients with: 1. alteration/alterations of treatment plan; 2. no alteration of treatment plan; and, 3. MRI-related conversion from BCS to mastectomy.

The predictive values were calculated with a logistic regression model. The groups entered the model by means of indicator variables and standard errors were obtained with the sandwich robust estimator. [20] Due to the logit link of logistic regression, the resulting confidence intervals were asymmetric and within the feasible probability interval zero to one. The sandwich estimator for the standard errors ensured that confidence intervals were consistently estimated while taking into account the potential intra-individual dependence in the data.

A receiver operating characteristic (ROC) curve was constructed for a positive finding using four ratings based on BI-RADS scores: BI-RADS 1/2, BI-RADS 3, BI-RADS 4 and BI-RADS 5. To include potential intra-individual dependence in the data, the confidence interval around the point estimate was calculated using 500 design-matrix bootstrap samples. [21] The resampling units were the individuals, not the single observations. For visual ease, the ROC curve was smoothed with a binormal likelihood model. [22] All analyses were performed in Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

Patients who received neoadjuvant treatment with unconfirmed pre-treatment incremental MRI findings and patients with a reported smaller tumor only i.e. without co-excisting IFs were excluded from statistical analyses.

3. Results

The index tumor in the affected breast was MRI-identified in 199 of 210 patients, either as a BI-RADS 4 or 5 lesion

With a cut-off of BI-RADS 4, the overall MRI sensitivity for identifying the index tumor was 95% (95% CI 91–97%). In eleven patients, (size range 7–55 mm, median 12 mm) the index lesion (eight pure DCIS, two IDC and one fibroadenoma) was not identified with certainty.

A review of the dataset identified an additional seven patients with IFs not described in the POMB trial.

Smaller index tumor were described in four patients, two with and two without co-existing IF, resulting in one conversion from mastectomy to BCS and one from neoadjuvant treatment to mastectomy.

In total, 88/210 (42%) patients presented incremental findings resulting in alteration of treatment plans in 41 (20%), (Fig. 2). In four of these patients, nodes was the sole incremental finding giving an abnormal interpretation rate of 40% of in-breast IF.

Ten patients with neoadjuvant treatment were excluded leaving 78 patients (39 with and 39 without altered treatments) eligible for statistical analysis.

Nighty nine in-breast IF were described. Their distribution, accuracy and in-breast BI-RADS scores are listed in Table 1.

Fifty-six (64%) of the 88 patients with IFs underwent a second-look US examination of breast and/or axilla targeted at one or more IFs resulting in 47 biopsies in 44 patients confirming 21 IF (including three lymph nodes) as malignant in 19 patients (Fig. 4).

Including BI-RADS 3, 4 and 5 findings the preoperative biopsy yield of malignancy, including diagnostic excisions for in-breast IF was 51% (21/41 patients). Corresponding results for BI-RADS 4 and 5 were 72% (21/29 patients)

At final histopathology the altered treatment plan/s were justified in 32/39 patients (82%) and unjustified in seven (18%) corresponding to 15% and 3,3% of the 210 patients examined.

Due to eleven MDT recommendations and two patient choices 13 out of 43 decisive incremental findings were unverified as malignant or high-risk lesions prior the effected treatment change/s (Tables 2 and 3). Three out of six biopsied high-risk lesions were, confirmed malignant after diagnostic excisions and one at final histopathology leaving one atypical ductal hyperplasia and one radial scar.

The *PPV* for the total number of IF was 74%: (95% CI 60–84%) in the group of patients with altered treatment and 27%: (95% CI 14–44%) in the group of patients without.

MRI related conversion from BCS to mastectomy were performed in 22 patients (Table 2). In 20 of these patients the decisive IFs were true positive, *PPV* = 91% (95% CI 69–98%).

The remaining MRI related treatment changes and associated decisive IF are listed in Table 3. The *PPV* for the decisive IF in Table 2 and 3 was 83% (95% CI 68–92%).

Histopathological incremental findings were identified in seven patients: in three mastectomized patients and in four patients after

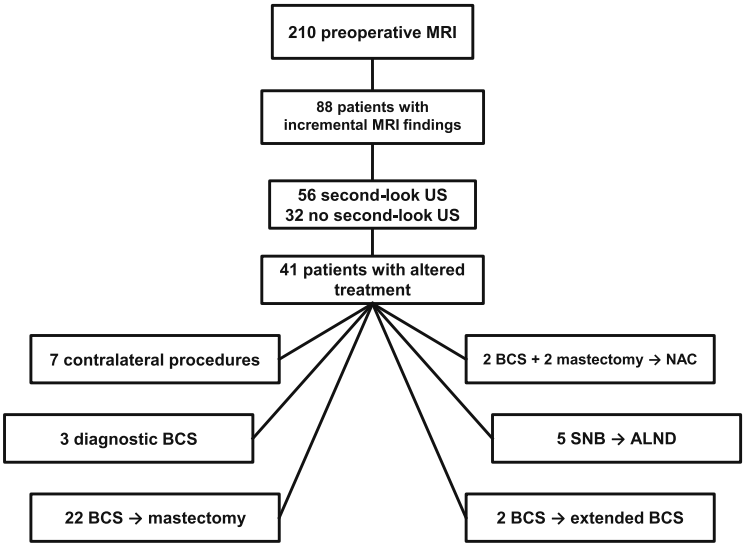

Fig. 2. Flow chart showing the number of MRI related additional diagnostic procedures and distribution of altered managements among 210 patients who underwent pre-operative breast MRI in the POMB trial.
Abbreviations; MRI = Magnetic Resonance Imaging, US = Ultrasound, BCS = Breast Conserving Surgery, SNB = Sentinel Node Biopsy, NAC = Neoadjuvant chemotherapy, ALND = Axillary Lymph Node Dissection

Table 1
Distribution of the incremental MRI findings, their accuracy, in-breast BI-RADS scores and nodes for patients with and without MRI related treatment alterations.

Altered Treatment (n = 39 Patients)

	BI-RADS								
	5		4		3				
Type of IF	TP	FP	TP	FP	TP	FP	Sum TP	Sum FP	Total
LT	6	3	4	1	0	0	10	4	14
MF	5	1	11	2	1	1	17	4	21
CL	2	0	2	1	0	5	4	6	10
Nodes	–	–	–	–	–	–	9	0	9
Sum	13	4	17	4	1	6	40	14	54

No Altered Treatment (n = 39 Patients)

	BI-RADS								
	5		4		3				
Type of IF	TP	FP	TP	FP	TP	FP	Sum TP	Sum FP	Total
LT	4	3	0	0	0	1	4	4	8
MF	1	1	4	8	1	5	6	14	20
CL	0	0	0	2	0	12	0	14	14
Nodes	–	–	–	–	–	–	2	1	3
Sum	5	4	4	10	1	18	12	33	45
Total	18	8	21	14	2	24	52	47	99

Abbreviations: LT = larger index Tumor, MF = Multifocality.
CL = Contralateral finding, TP = True Positive, FP = False Positive.
IF = Incremental Finding.

reoperation due to positive surgical margins, thus leaving 115 patients considered true negative with respect to IF (*NPV* = 94% (95% CI 89–97)).

The empiric area under the receiver operating characteristic curve (AUC) for the incremental in-breast findings was 85% (95% CI 78–91%). The associated ROC curve are presented in Fig. 3.

4. Discussion

In this patient sample of 210 women ≤56 years who underwent preoperative breast MRI in the POMB trial we reached high diagnostic accuracy of the IFs with impact on therapeutic approaches.

Apart from the potential to alter in-breast treatments in patients eligible for breast conserving surgery, incremental MRI findings can also influence decisions of the contralateral breast, axillary approaches and use of neoadjuvant therapy [14–16].

A major strength of our results is that they are extracted from a randomized controlled trial performed in an overall clinical setting including patients with both screening and clinically detected breast cancers scheduled for different treatment plans.

The subgrouping of the IFs into those decisive for alterations of initial treatment plans correlates to recommendations made by pre-treatment MDTs and is related to the outcomes in the POMB trial.

However, accuracy measurements such as predictive values and AUCs is dependent on the prevalence of disease [23,24] implicating that comparisons with data established from other study populations should be interpreted with caution.

Another important factor with impact on accuracy is the choice of evaluation criteria for the IFs and various approaches regarding this exists in the literature. The choice of evaluation criteria for the IFs in this study were based on their relation to overall tumor burden and impact on prognosis [25,26].

In a prospective single-institutional study - including 465 patients - investigating preoperative performance of breast MRI Camps et al [27] reached similar results as in the present study with respect to biopsy yield and justifiable changes of therapeutic approach.

The conversion rate from BCS to mastectomy in the ipsilateral breast due to true positive and false positive IFs was similar to those presented by Houssami [[28]] et al in their meta-analysis of 19 pre-operative studies of women with newly detected breast cancer recieving preoperative MRI.

Apart from being a relatively small study, some other limitations need to be, addressed.

In some of the patients with MRI related treatment changes the decisive IFs were unverified prior to treatment. This discordance with

Table 2
Decisive IF and tumor sizes in 22 patients with MRI related conversion from BCS to mastectomy, pre-operative biopsy results (fine needle aspiration if not otherwise specified) and tumor size in final histopathology. In the column "Confirmed decisive IF" a "Yes" is considered true positive finding confirmed either pre- or post-treatment or both.

		Sec. look	Biopsy	Size [mm]					
Age at randomization	Decisive IF	US	result	MG	US	MRI	Histopathology	Confirmed IF	Histopathologic Phenotype
45	MF	No	–	33	17	38 + 22 + 7	75	Yes	ILC
50	LT	No	–	10	0	65	100	Yes	DCIS
50	MF	Yes	Cancer	10	0	14 + 7 + 3 + 20	50	Yes	IDC + DCIS
38	LT	Yes	Cancer	0	5	65	53	Yes	IDC + DCIS
40	MF	Yes	Cancer	15	14	23 + 16	18 + 17	Yes	IDC
41	LT	Yes	Cancer	0	0	51	50	Yes	IDC + DCIS
48	MF	Yes	Atypia	30	21	24 + 13 + 9+6	66	Yes	IDC + DCIS
43	MF	No	–	30	29	32 + 10	32 + 13	Yes	IDC + DCIS
34	LT	Yes	Benign	10	10	43	65	Yes	IDC
45	MF	Yes	Cancer	0	16	17 + 10	15 + 18	Yes	IDC + DCIS
49	LT	Yes	IDC[1]	0	40	78	80	Yes	IPC + DCIS
51	MF	Yes	Cancer	30	18	17 + 8	17+15	Yes	IDC + DCIS
46	MF	Yes	Cancer	15	10	10 + 8	10 + 4 + 4	Yes	IDC + DCIS
46	MF	Yes	Cancer	20	0	23 + 7+5	19 + 8	Yes	IDC + DCIS
54	MF	Yes	IDC + DCIS[2]	12	12	11 + 9	12 + 7	Yes	IDC + DCIS
43	MF	Yes	Cancer	10	7	36 + 6+7	8 + 5 + 8	Yes	IDC + DCIS
48	MF	Yes	Cancer	28	15	17 + 11 + 5 + 5	24 + 10 + 6+10	Yes	IDC + DCIS
47	LT	No	–	0	40	70	70	Yes	IDC + DCIS
54	LT	No	–	18	0	65	90	Yes	IDC + DCIS
50	LT	Yes	DCIS[1]	15	10	27 + 3 foci	30 + 70	Yes	IDC + DCIS
44	MF	Yes	0	0	15	13 + 8+6	15	No	IDC
55	MF	Yes	Benign	15	20	25 + 50	19	No	IDC

Abbreviations: LT = Larger index Tumor, MF = Multifocality, IF = Incremental Finding, US = Ultrasound, MG = Mammography, IDC = Invasive Ductal Carcinoma, ILC = Invasive Lobular Carcinoma, IPC = Invasive Papillary Carcinoma.
[1] Core needle biopsy.
[2] MRI Guided Vacuum Biopsy.

Table 3
Decisive IF and their associated treatment changes, pre-treatment biopsy results (fine needle aspiration if not otherwise specified) and tumor sizes at mammography, ultrasound, MRI and histopathology. In the column "Confirmed decisive IF" a "Yes" is considered true positive finding, confirmed either pre- or post-treatment or both.

		Sec. look	Biopsy	Size [mm] (axillary node+/nodes)					
Age at randomization	Decisive IF	US	result	MG	US	MRI	Histopathology	Confirmed Decisive IF	Histopathologic Phenotype
DIAGNOSTIC SURGERY (Ipsilateral Breast)									
51	MF	Yes	Atypia	20	18	20 + 28	20 + 28	Yes	ILC
44	MF	Yes	Atypia	0	5	5 + 45 + 8	20 + 25	Yes	IDC + DCIS
50	MF	Yes	Atypia	16	18	15 + 12	13 + 4	Yes	IDC + DCIS
EXTENDED RESECTION									
38	LT	No	–	20	23	60	28	No	IDC
52	MF	No	–	10	0	17 + 25	5	No	DCIS
CONTRALATERAL SURGERY									
44	CL	Yes	Cancer	–	–	33 + 15 + 11	23	Yes	IDC
43	CL	Yes	IDC[1]	–	–	35	15 post NAC	Yes	IDC
55	CL	Yes	IDC[1]	–	–	13 + 14 + 10	40	Yes	IDC
50	CL	Yes	Cancer	–	–	10	9	Yes	IDC
45	CL	Yes	ADH[1]	–	–	35	3 post NAC	No	ADH
42	CL	Yes	Benign	–	–	5	–	No	SA
37	CL	Yes	Atypia	–	–	16	15	No	RS
NEOADJUVANT TREATMENT									
37	LT + Node	Yes	Cancer[2]	20	15	60	30 post NAC	Yes	IDC
50	LT	No	–	25	25	76	40 post NAC	–	IDC
40	LT	No	–	0	31	52	6 post NAC	–	DCIS
41	LT + Node	Yes	Cancer[2]	0	40	80	29 post NAC	Yes	IDC + DCIS
AXILLARY SURGERY									
53	Node	Yes	Cancer	15	15	60	20 (3+/17)	Yes	IDC
40	Node	Yes	Cancer	14	14	17	20 (3+/17)	Yes	ILC
42	Node[3]	Yes	Cancer	15	16	12	13 (0+/10)	Yes	IDC
55	Node	No	–	35	40	32 + 4	35 (2+/12)	Yes	IDC
54	Node	No	–	40	30	23	25 (7+/12)	Yes	IDC

Abbreviations: LT = larger index Tumor, MF = Multifocality, IF = Incremental Finding, US = Ultrasound, MG = Mammography, IDC = Invasive Ductal Carcinoma, ILC = Invasive Lobular Carcinoma, RS = Radial Scar, ADH = Atypical Ductal Hyperplasia, SA = Sclerosing Adenosis, NAC = Neoadjuvant chemotherapy.
[1] Core Needle Biopsy.
[2] Palpation Guided Biopsy of Node.
[3] True Positive Parasternal Node.

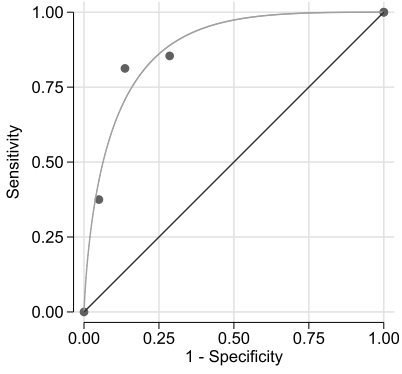

Fig. 3. Receiver Operating Characteristics curve and empiric data (dots) for the incremental findings in the MRI group in the POMB trial. Empiric AUC = 85% (95% CI 78–91%).

guidelines [3,4] were due to MDT recommendations based on the level of suspicion on initial imaging and patient choice.

Boarder-line candidates for BCS might also have influenced the MDT recommendations for unverified treatment changes. Furthermore, MRI-guided biopsy was introduced late in the trial and only four such procedures were performed.

Elevated background parenchymal enhancement, BPE has been shown to be associated with increased abnormal interpretation rate, young age and higher rate of BI-RADS 3 assessments [29,30]. Since the included patients were younger than 56 years the proportion of elevated BPE and reported BI-RADS 3 findings is assumed to be higher in this trial compared to studies including wider age-spans of patients.

We identified seven patients with false negative IFs. This number is most probably an underestimate of the true value in this setting, particularly with respect to DCIS [31] implicating that the presented AUC value should be interpreted with some caution.

In total, seven (3,3%) of the patients participating in the study underwent unjustified treatment alterations due to false positive IFs. According to final histopatology results a more consistent use of second-look US and MRI guided biopsies would not have reduced this number any further in this trial. Although interpretation of breast MRI is highly radiologist dependent [[32]] it is important to acknowledge the method as a complement to other breast diagnostic modalities and that the final outcome with respect to any alteration of treatment should be related to the complete diagnostic and clinical situation presented at MDT.

In summary, our study illustrates what might be expected in terms accuracy of incremental findings when preoperative breast MRI is introduced in an overall clinical setting among patients with newly detected breast cancer. The results implicates that around 15% of the patients in the control group in the POMB trial were denied adequate initial treatments with impact on prognosis. Further investigation will show, whether this could be translated into improved long-term survival and/or reduced recurrence rates.

5. Conclusion

We conclude that breast MRI, performed and evaluated together with conventional breast imaging methods provides relevant incremental information at a high degree of accuracy in the pre-operative setting.

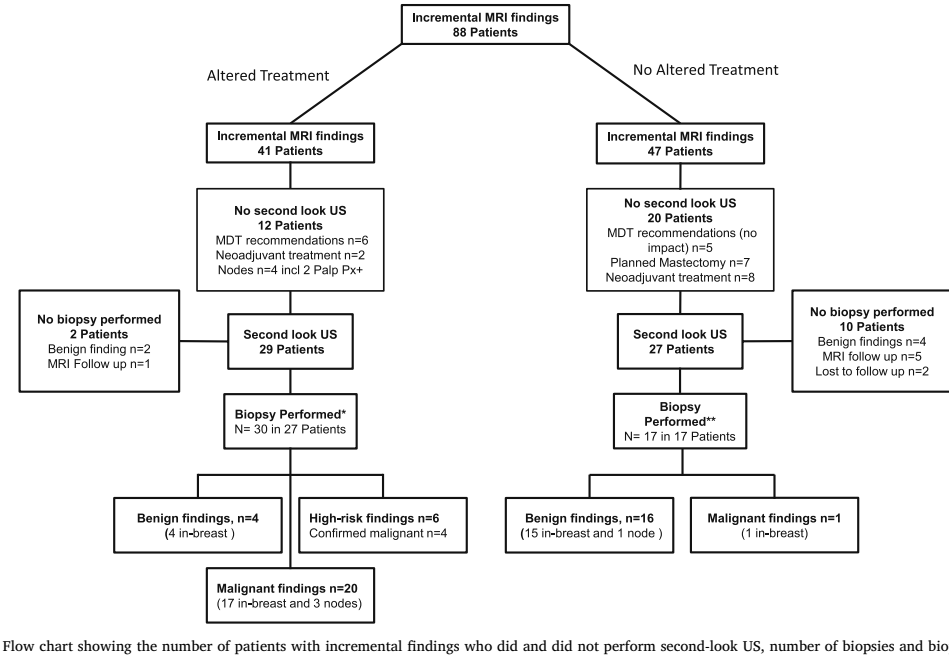

Fig. 4. Flow chart showing the number of patients with incremental findings who did and did not perform second-look US, number of biopsies and biopsy yields.
* Including one confirmed MRI guided biopsy.
** Including three benign MRI guided biopsies.

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Potential and real conflicts of interest

The authors declare no conflict of interest.

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Paper III

Original article

Preoperative MRI in women with newly diagnosed breast cancer: re-excision rates and additional findings

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Abstract

Background: Preoperative breast magnetic resonance imaging (MRI) is still controversial as an adjunct to conventional breast cancer workup in terms of the effect on re-excision rates. Our objective was to analyse whether the introduction of preoperative breast MRI influences the rate of re-excisions in women with newly diagnosed breast cancer and to study the additional ipsi- and contralateral MRI findings and their impact on surgical management.

Methods: Women with newly diagnosed breast cancer having preoperative MRI and surgery at Vastmanland County Hospital Breast Unit from January–June 2018 (n = 84) were compared with women not undergoing preoperative MRI from January–June 2016 (n = 97). Data were collected from retrospective reviews of patients' medical records.

Results: The re-excision rate was one of 84 (1.2%) in 2018 and three of 97 (3.1%) in 2016. There was no statistically significant difference in re-excision rates between the two study periods. In the MRI cohort, seven patients of 84 (8%) had malignancy in the ipsilateral and two (2%) in the contralateral breast not previously detected by conventional imaging. Additional malignant findings were more common in women of age < 59 years, and more often resulted in mastectomy.

Conclusions: Preoperative breast MRI in women with newly diagnosed breast cancer did not reduce the number of re-excisions. Additional malignant findings were more common in women younger than 59 years and influenced surgical management. MRI resulted in no delay of surgery.

Introduction

Since the introduction of magnetic resonance imaging (MRI) into clinical practice in the late 1980s, its role as a preoperative diagnostic tool, and whether to use it has been controversial[1,2] Breast MRI provides images with a higher sensitivity than mammography (MG) but at a lower specificity. According to previous studies, the sensitivity of breast MRI is around 90–95%. The specificity, however, is only 72–75%, which entails a risk of benign lesions being mistaken for malignant ones[3].

The European Society of Breast Cancer Specialists (EUSOMA) working group has formulated guidelines for when to use MRI in clinical practice. Among these, the use of preoperative breast MRI is recommended in women under 60 years of age when the size of the identified lesion, measured using MG and ultrasonography (US) differs by more than 1 cm[4].

Accurate preoperative determination of breast cancer extent can be a valuable guide to surgical planning to avoid the presence of tumour cells at the surgical resection margin and re-excision. Re-excision is associated with increased risk of complications and increased costs, both for the health care service and for society in the form of prolonged hospital stays and increased anxiety levels in distressed patients[5]. Re-excision is also often a more challenging surgical procedure due to changes in the initial anatomy and leads to a poorer aesthetic result[6]. Furthermore, a meta-analysis of 22 studies has shown that MRI can be used for detecting occult breast cancer in the contralateral breast[7].

However, there are disadvantages with MRI that should be noted. Because of its high sensitivity and moderately low specificity, MRI is an imaging method that may lead to an unnecessarily high number of additional invasive investigations, such as core biopsies and follow-ups with false-positive results, while excluding malignancy. Previous studies have

shown that the use of MRI prolongs the time to treatment and increases the likelihood of mastectomy because of additional findings[8].

MRI is an expensive method, with a cost of € 400, according to the pricelist of 2019 in the Department of Radiology, Vastmanland County Hospital[9]. This cost is approximately 5 times higher than a diagnostic mammogram and therefore leads to increased costs for the health care service. MRI is also time-consuming, and it requires that patients lie still, which might cause discomfort or be problematic in those with claustrophobia. Gadolinium contrast required for enhancement of tumours to highlight neovascularity, enabling differentiation of benign from malignant breast tissue[1], is known for its potential to cause nephrogenic systemic fibrosis, allergic anaphylactoid reactions and deposits in organs such as the brain[10-13]. MRI cannot be performed in patients with magnetic resonance unsafe devices such as certain implants[14].

To our knowledge, there are only four larger randomized controlled trials published regarding preoperative MRI in women with newly diagnosed breast cancer, and they show contradictory results. In the 2010 COMICE multicentre study by Turnbull et al.[15], 1623 women were randomly assigned to either MRI or no further imaging. It was found that preoperative breast MRI in addition to conventional workup was not significantly associated with reduced re-excisions and might be unnecessary[15]. In the MONET study from 2010 which included 418 women, preoperative MRI was evaluated in terms of improvement in management in addition to MG and/or US in patients with nonpalpable suspicious breast cancer. MRI was unexpectedly found to be associated with an increased re-excision rate[16]. The Swedish multicentre POMB study randomized 440 women aged 56 years and younger with newly diagnosed breast cancer to undergo either preoperative breast MRI in addition to standard of care or standard of care alone. In contrast to prior studies, the results showed that having an MRI decreased the rate of re-excision by 30% without increasing the number of

mastectomies[17]. Another prospective randomized trial from Finland included 100 patients. In the group of patients who undertook preoperative MRI, the re-excision rate was 14% and 24% in the control group. However, the difference was not statistically significant ($P = 0.202$)[18.]

Previous randomized studies have thus shown conflicting results and more research has been requested by colleagues. MRI has evolved and recent technological advances have optimized the MRI technique. MRI with an increased main magnetic field at 3 Tesla (T) instead of the previous 1.5 T can improve spatial and contrast resolution[19]. In Vastmanland County Hospital a 3 T MRI has been in routine use since 2018.

The primary aim of this study was to determine if the introduction of MRI in the routine management of breast cancer patients has influenced the rate of re-excisions. Secondary aims were to study additional malignant findings in the ipsi- and contralateral breast, type and timing of surgery.

Methods

This study is a single-centre retrospective cohort study comparing breast cancer patients diagnosed in 2016 with those diagnosed in 2018. Data were collected at the Breast Unit, Vastmanland County Hospital, Vasteras, by retrospective review of patients' medical records including clinical characteristics, radiological, surgical and histopathological results. The MRI group included all women with newly diagnosed breast cancer who had undergone conventional investigation (MG, US and clinical evaluation) between the 1st of January and 30th of June 2018. The decision to refer patients for a preoperative MRI examination was made by the breast radiologist. The patients in the control group were all women with newly diagnosed breast cancer between the 1st of January and 30th of June 2016. They were managed according to the standard of care alone. Time of management was measured from the day of first imaging until surgical treatment.

Repeat surgery within 2 months from initial surgery was considered as a re-excision. Patient data concerning re-excisions was retrieved from patient records and double-checked against the National Quality Register for Breast Cancer (NKBC), where information regarding treatment and complications is registered. It has been in use since 2007 to collect essential data from all treated cancer patients in Sweden[20]. Data from Vastmanland County, Stockholm County and the whole country regarding re-excision and one single operation was retrieved (Appendix 1).

Ethical considerations

The study was approved by the regional research ethics committee in the Uppsala–Orebro region, Dnr 2018/260. This study is a retrospective quality assurance study; hence, the patients were not specifically invited to participate in this study. However, all patients were asked if they were willing to undergo breast MRI at the time of the initial investigation. They have all given their permission to store biomarkers and personal data for research purposes.

Statistical methods

Data management and analyses were conducted using the IBM Statistical Package for Social Sciences (SPSS™) software (IBM Corp., Armonk, NY, USA). To compare the mean age and body-mass index between the groups, a two-sided *t* test was used to test for significance. To investigate the relationship between the surgical treatment, palpable lesion, metastases, neoadjuvant treatment, re-excision and preoperative MRI, Fisher's exact test was used. The significance level was set to $P < 0.05$.

MRI procedures

All MRI examinations were performed on a 3-Tesla Philips Magnetic Resonance imaging unit (Philips Healthcare, Amsterdam, the Netherlands) with contrast enhancement. Both breasts

were routinely imaged and independently assessed by two radiologists using the Breast Imaging-Reporting and Data System (BI-RADS) scale[21].

Results

Recruitment of the study population in the MRI group is presented in Figure 1. Preoperative breast MRI was performed in 166 patients between the 1st of January and 30th of June 2018. Among those, 86 patients had newly diagnosed breast cancer. One patient died before surgery and one had only neoadjuvant chemotherapy, thus 84 had surgery. During the time period, 123 patients in total were diagnosed with breast cancer. Thirty-seven patients did not undergo preoperative breast MRI for the following reasons. Three patients declined, 15 had a tumour size ≤ 10 mm, 12 patients had a contraindication to MRI and in seven patients, MRI would not have contributed to any altered treatment regardless of new findings.

All patients having surgical treatment for breast cancer between the 1st of January and 30th of June 2016, n = 97, were selected for comparison.

Patient characteristics, clinical and treatment data of patients treated with surgery are presented in Table 1. Patients who had an MRI were slightly younger, leaner and were treated with neoadjuvant chemotherapy to a greater extent.

Histological and clinicopathological data from all breast cancer cases are presented in Table 2. There were four patients with bilateral cancer in the 2018 group and three patients in the 2016 group. Lobular invasive carcinomas and ductal carcinoma in situ (DCIS) were more frequent in the group of patients included from 2018. Ductal invasive carcinomas and oestrogen-receptor positive cancers were more common in the 2016 group.

Rate of re-excision

There was only one re-excision among 84 patients (1.2%) in the MRI group versus three re-excisions in 97 (3.1%) in the no MRI group. The difference was not statistically significant, $P = 0.625$.

Additional findings in the MRI group

Preoperative MRI findings are presented in Figure 2. There were additional malignant findings in the ipsilateral breast in seven patients not previously detected by conventional imaging (MG or US). Core biopsy was most commonly used for diagnosis. Two patients had malignant findings in the contralateral breast.

In a subgroup analysis of younger patients (<59 years), additional findings were present in 7 of 28 patients in this population compared with 2 of 49 in the older patients. The younger patients were also more often subjected to mastectomy, 16 of 34 vs. 12 of 50 in the older patients, ($P = 0.025$).

Among the patients in the MRI group receiving neoadjuvant treatment, all except one patient planned for surgery had a mastectomy. Two patients had additional findings on MRI, but only in one of them did the MRI have sufficient impact to alter the treatment plan. Seven patients (three in the ipsilateral and four in the contralateral breast) had additional MRI findings which were not confirmed to be malignant on biopsy.

Timing of surgery

The mean time of management from first imaging to surgery was 32.8 and 30.5 days in the MRI group and the no MRI group, respectively (range 17–84 and 8–71, respectively), ($P = 0.214$). Eleven patients in the MRI group and four in the no MRI group had neoadjuvant chemotherapy and were not included in this calculation.

In addition, there was no statistically significant difference in the mean-time of management from first imaging to surgery among patients receiving neoadjuvant chemotherapy. Times were 135.9 days in the MRI group and 138.0 days in the no MRI group (range 25–181 and 69–176, respectively), (P = 0.948), Table 1.

Discussion

Preoperative breast MRI as a complement to conventional workup did not alter the rate of re-excision in breast cancer patients despite additional MRI findings not previously detected by conventional imaging. Biopsy-verified malignancy was found in 10% of patients in the ipsi- or contralateral breast. Additional findings were present mainly in women younger than 59 years and were associated with a higher rate of mastectomy. On the other hand, 7 of 16 biopsy-verified MRI findings proved to be benign, which reflects the negative aspect of MRI with its rather low specificity and need for further diagnostic workup. The re-excision rates were generally low in both groups, 1.2% in the MRI group vs. 3.1% in the no MRI group, compared with previously published studies where rates varied between 10% and 60%[22, 23].

The re-excision rates found in our trial are corroborated by data from the INCA registry (Appendix 1). Data are summarized from 2009–2017 from patients treated with only one operation (no re-excision because of tumour data) in Vastmanland County, Stockholm County and the nation. There was a dramatic change in Vastmanland County between 2012 and 2013 when there was a reduction of re-excision rates from 9% to 2%. The underlying reason could not have been improved local staging with MRI, because more consistent MRI use was introduced later in 2016. A plausible reason for this major change might rather have been new international guidelines regarding surgical margins announced in St. Gallen in January 2013. The guidelines included new recommendations for surgical margins that were, no tumour on ink for invasive carcinoma and margins no less than 2 mm for DCIS[24, 25] instead of the more extensive margins previously advocated. There is thus little room for further improvement in

terms of re-excision, as pointed out by D. David Dershaw in an editorial published in the Breast Journal in 2016 where he states, 'an examination of the successfulness of breast-conserving treatment demonstrates the room for improvement is narrow'[26].

With a study population comparable to our report, a retrospective study from the United States by Patel et al. (2015) compared 96 patients with 154 patients who underwent preoperative MRI or not, respectively. The re-excision rates were higher in the control group 24 out of 96 (25%) compared with 11 out of 154 patients (7.1%) in the MRI group, a statistically significant difference ($P < 0.001$)[27]. Similarly, the Swedish POMB study conducted between 2007 and 2011, included 440 patients of whom 220 were randomized to preoperative MRI. The results also showed a statistically significantly lower rate of re-excision in the no MRI group, 5% in the MRI group vs. 15% in the no MRI group[17]. The lack of a significant difference in our present study could thus be an effect of a generally low number of events and we cannot rule out a true difference.

A systematic review and meta-analysis by Houssami et al. published in 2008 included data from 19 studies on 2610 women with breast cancer and showed that MRI detects additional disease with a median of 16% (range 6%–34%)[28]. In a study by Killelea et al. (2013), preoperative MRI revealed malignancy in 8% of patients in the ipsilateral breast, 2% in the contralateral and 1% in both[29]. Comparable data are seen in a study by Lehman et al. (2007) where MRI detected occult cancer in the contralateral breast not seen on mammography or clinical evaluation in 3%[30]. Schell et al. (2009) included 199 patients with newly diagnosed breast cancer who underwent preoperative MRI. Imaging detected 74 patients (37%) with suspicious, previously unknown lesions. Thirty-eight patients (19%) had malignant findings consisting of 44 lesions of which 41 were invasive[31]. In the randomized controlled trial from Finland (2018) that included 100 patients, 50 patients in the MRI arm revealed that 14 (28%) had additional findings. Seven (14%) biopsy-verified malignant

findings were found, six in the ipsilateral and one in the contralateral breast[18]. By comparison, MRI in our study found nine (10%) new malignancies in 86 patients not previously detected by conventional imaging. These findings were predominantly observed in patients of a younger age (<59 years). Dense breast tissue often found in the younger population might be a reason why malignant lesions are less likely to be detected by conventional imaging but revealed on MRI because of its higher sensitivity. Although it was not shown that the younger patient population in the POMB study had denser breast tissue than the population in general, preoperative MRI had an impact on the re-excision rate due to the high number of additional lesions found[17].

Moreover, the Finnish study noted that the mean number of days from referral to surgery was 34 days in the MRI group and 21 days in the control group ($P < 0.001$)[18]. In our study, we found that the mean number of days between the cohorts from first imaging to surgical treatment differed by only 2 days and therefore did not significantly delay the time to surgical treatment, as a previous study has shown[8]. Our data suggest that preoperative breast MRI is well incorporated in the investigation process in Vasteras Breast cancer unit.

A limitation of this study is the small sample size of each group with few events, in part due to a well-functioning breast team and health care system and the fact that it is a retrospective study. In addition, the demographic data in the groups are not entirely balanced. The mean age of patients in the MRI group was four years lower than in the no MRI group. A reason for this might be that the general guidelines state that MRI should be conducted in women younger than 60 years because these patients tend to have denser breast tissue. There was also a larger proportion of patients in the MRI group receiving neoadjuvant chemotherapy, possibly correlated to patients at a younger age but also to the increasing popularity of neoadjuvant treatment due to supposedly improved overall survival because of earlier initiation of systemic therapy of high-risk patients. It has also been recognized that

younger women are more likely to achieve a pathologic complete response with neoadjuvant chemotherapy[32]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) summarized data from 4756 women in 10 trials between 1983 and 2002[33] stating that there were no significant differences between neoadjuvant chemotherapy vs. adjuvant chemotherapy in the risk of distant recurrence or breast cancer mortality. The main goal of neoadjuvant chemotherapy from a surgical perspective is to downstage the tumour and to reduce metastatic burden. The EBCTCG reported that the use of neoadjuvant chemotherapy was associated with an increased frequency of tumour downstaging, facilitating breast-conserving surgery but also with an increased risk of local recurrence attributed to the less radical surgical approach. In contrast, the results from our study suggest that downstaging was only possible in three of 15 patients receiving neoadjuvant chemotherapy and while preoperative breast MRI did add new information, it altered treatment in only one patient.

Preoperative breast MRI has several advantages because of its high sensitivity in detecting occult breast cancer in the ipsi- and contralateral breast as well as determining tumour extent, especially in women with dense breasts[3, 4]. It could be assumed that accurate local staging leads to improved treatment and improved short- and long-term outcomes. The few randomized trials published have evaluated preoperative MRI in several aspects, but with inconclusive results. In our study, preoperative MRI does not improve surgical outcome in terms of reduction in re-excision rate despite the detection of additional disease. Critics argue that smaller unidentified cancers might not become biologically active or are successfully treated with radiation if not surgically removed[8, 34]. Because of additional MRI costs, complementary investigation and potentially more aggressive surgery[8], it is consequently of major importance to address the absence of long-term data that describe the effect of preoperative breast MRI in terms of breast cancer recurrence and survival.

Conclusions

Preoperative breast MRI did not affect the rate of re-excision in women with newly diagnosed breast cancer. However, important additional malignancies were found, mainly in younger women who were more often subject to mastectomy. MRI resulted in no delay of surgery.

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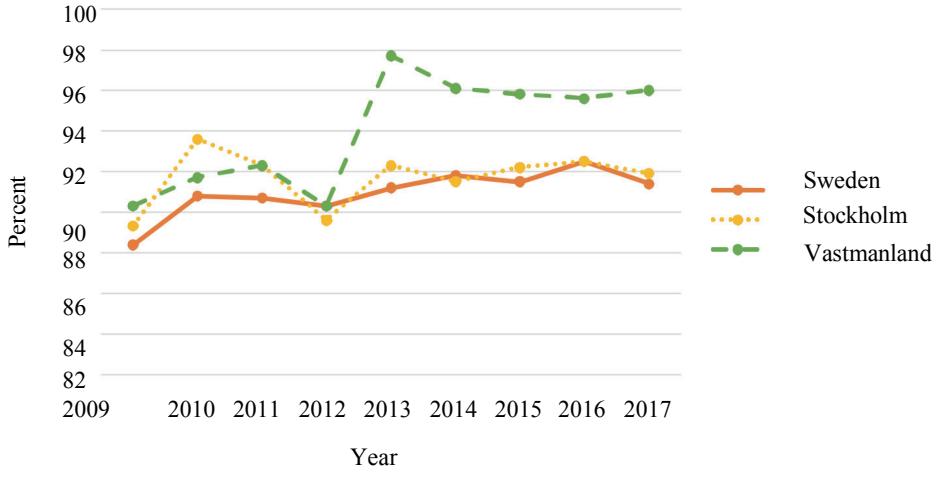
Appendix



Appendix 1. Data from NKBC on frequency of a single operation between 2009-2017 in Sweden, Stockholm and Vasteras.

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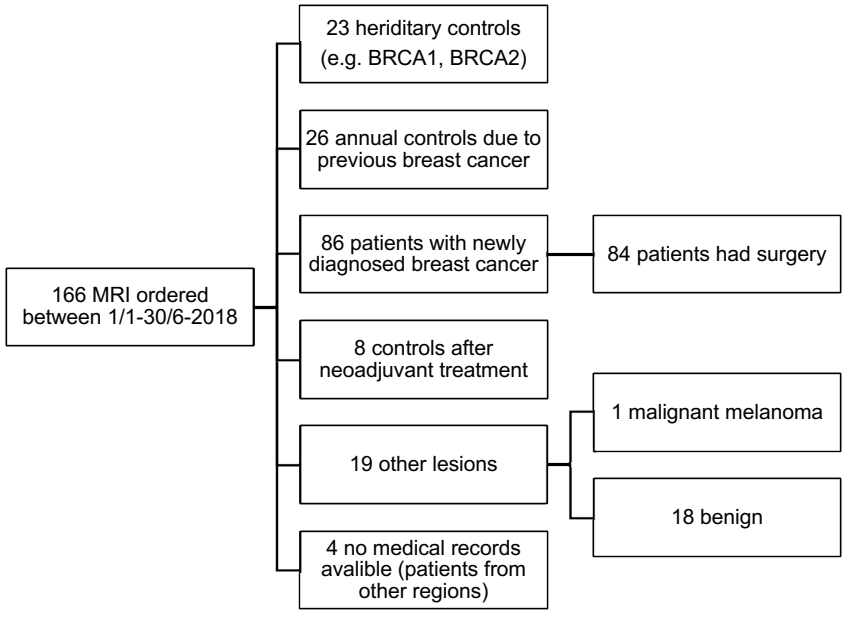

Fig. 1 The total number and indications for preoperative breast MRI 1/1–30/6 2018.

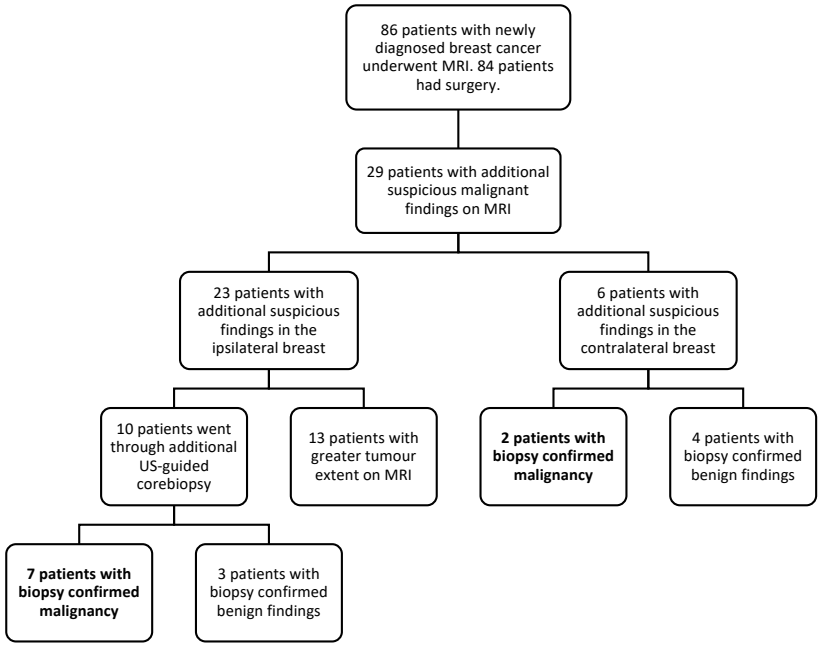

Fig. 2 Additional findings in the MRI group. The boxes in bold show that MRI findings, not previously seen on mammography, were malignant in nine patients.

Table 1. Patient´s characteristics: clinical and treatment data from included patients 1/1–30/6 2018 and 1/1–30/6 2016.

	MRI (Jan–Jun 2018) (*n = 84) (46.4%)*			**No MRI** (Jan–Jun 2016) (*n = 97) (53.6%)*			
	n	(%)	mean/range	*n*	*(%)*	*mean/range*	*P-value*
Body Mass Index (kg/m2)			25.4 (17.6–37.5)			28.4 (17.7–42.30)	*P*<0.05
Age at diagnosis (years)			59.3 (30–80)			64.7 (40–86)	*P*<0.05
Surgery							*P*=0.148
BCS	54	64.3%		72	74.2%		
Mastectomy	28	33.3%		25	25.8%		
Only axillary clearance	2	2.4%		0	0%		
No axillary surgery (e.g. DCIS❖)	9	10.7%		7	7.2%		
Axillary surgery							*P*=0.357
Sentinel Node	59	70.2%		79	81.4%		
ALND	15	17.9%		10	10.3%		
SNB + ALND♠	1	1.2%		1	1.0%		
***No.* days between first imaging and surgery**			32.8 (17–84)			30.5 (8–71)	*P*=0.214
***No.* days between first imaging and surgery (neoadjuvant group)**			135.9 (25–181)			138 (69–176)	*P*=0.948
Palpable lesion							*P*=0.495
Yes	46	54.8%		58	59.8%		
No	38	45.2%		39	40.2 %		
Neoadjuvant therapy							P=*0.029*
Yes	11	13.1%		4	4.1%		
No	73	86.9%		93	95.9%		
Metastases							P=0.865
Yes	25	29.8%		30	30.9 %		
No	59	70.2%		67	69.1 %		
Patients with bilateral cancer	4	4.5%		3	3.1%		P=0.561

❖DCIS = Ductal carcinoma in situ, ♠ALND = Axillary lymph node dissection.

Table 2. Histological and clinicopathological data of the carcinomas found in MRI and no MRI groups

	MRI (*n* = cases in 84 patients)		median (min–max)	**No MRI** (*n* = cases in 97 patients)		median (min–max)	***P*-value**
Ductal invasive carcinoma	52	59.1%		87	87.0%		*P*=0.000
Lobular invasive carcinoma	13	14.8%		6	6.0%		*P*=0.040
Ductal in situ	19	21.6%		7	7.0%		*P*=0.003
Lobular in situ	2	2.3%		0			*P*=0.218
Other							
Adenocarcinoma	1	1.1%		0	0.0%		*P*=0.468
Paget's	1	1.1%		0	0.0%		*P*=0.468
Total number of findings	88			100			
Tumour size mm, excluding neoadjuvant			17 (4–90)			15 (1–68)	
Tumour extent mm, excluding neoadjuvant			22.5 (4–115)			23 (3–100)	
ER*							*P*=0.000
Positive	58	65.9%		78	78.0%		
Negative	8	9.0%		15	15.0%		
No breast panel or DCIS	22	25.0%		7	7.0%		
PR☆							*P*=0.566
Positive	44	50.0%		62	62.0%		
Negative	22	25.0%		31	31.0%		
No breast panel or DCIS	22	25.0%		7	7.0%		
HER2*							*P*=0.319
Positive	8	9.1%		13	13.0%		
Negative	58	65.9%		80	80.0%		
No breast panel or DCIS	22	25.0%		7	7.0%		
Ki67							*P*=0.376
>20%	23	26.1%		29	29.0%		
<20%	43	48.9%		64	64.0%		
No breast panel or DCIS	22	25.0%		7	7.0%		

*ER = Estrogen Receptor, ☆PR = Progesterone Receptor, *HER2 = Human Epidermal Growth Factor Receptor 2.

Paper IV

Original Article

Impact of preoperative breast MRI on 10-year survival outcome of patients included in the Swedish randomised multicenter POMB trial

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Conflict of interest

The authors declare no conflict of interest.

ABSTRACT

Background: The value of preoperative breast magnetic resonance imaging (MRI) as an adjunct technique regarding its effect on re-excision rates has been a subject of discussion. No survival data regarding preoperative breast MRI are available from randomised studies.

Methods: Ten-year follow-up of the previous randomised multicentre study (POMB) was reported, evaluating MRI and its effect on disease-free survival (DFS) and overall survival (OS). A total of 440 patients with newly diagnosed breast cancer were randomised to either preoperative MRI (n = 220) group or conventional imaging (n = 220; control) group. Kaplan–Meier plots were used to analyse DFS and OS. Cox regression was used to estimate hazard ratios (HRs).

Results: The median follow-up time for each group was 10 years. DFS rates were 85.5% and 80.0% for the MRI and control groups, respectively (P = 0.099). The risk of relapse or death was 46% higher in the control group (HR 1.46, 95% confidence interval 0.93–2.29). OS rates after 10 years were 90.9% and 88.6% for the MRI and control groups, respectively (P = 0.427). The risk of death was 27% higher in the control group (HR 1.27, 95% confidence interval 0.71–2.29). Locoregional, distant, and contralateral recurrence outcomes combined, were increased in the control group (P = 0.048). A subgroup analysis of patients with breast cancer stages I–III showed that preoperative MRI improved DFS compared with conventional imaging but this did not reach statistical significance (P = 0.057).

Conclusion: After 10 years of follow-up, preoperative breast MRI as an adjunct to conventional imaging resulted in slightly, but non-significantly, improved DFS and OS.

ClinicalTrials.gov Identifier: POMB NCT01859936

INTRODUCTION

Surgical treatment for breast cancer has become less invasive after several randomised studies showed that breast conserving surgery (BCS) followed by radiotherapy for local control provides survival equivalent to that observed with mastectomy for invasive breast cancer[1–3]. Furthermore, studies have even reported poorer survival for patients who receive mastectomy than those who receive BCS and radiotherapy[4–8]. Preoperative evaluation using adequate imaging techniques to determine tumour size and extent within the affected breast facilitates surgical planning to avoid positive tumour margins and additional surgery. Re-excision is associated with greater risk of complication, increased patient anxiety levels, more challenging surgical procedures, delayed initiation of adjuvant therapies, and increased medical costs[9–10].

Presently, magnetic resonance imaging (MRI) is deemed the most sensitive method for detecting occult findings in the ipsilateral and contralateral breast in the preoperative setting, especially for women with dense breasts. However, preoperative breast MRI results in an increased proportion of false-positive findings requiring further investigation. This imaging modality is resource- and time-consuming, may increase patient anxiety, and can lead to unnecessary mastectomies[11,12]. Whether all MRI-detected additional findings that may have caused changes in previous treatment plans are in fact biologically relevant remains unclear[13].

Only a few randomised studies have evaluated the effect of preoperative MRI, albeit with inconclusive results[14–16]. The POMB (preoperative MRI of the breast) study, evaluated the effect of MRI findings on surgical decision making.[17] In contrast to other studies, it showed that preoperative breast MRI did result in altered treatment in 20 per cent of the patients and a reduction of re-excision rate by 30 per cent without an increase in the total number of mastectomies compared with conventional imaging. In a follow-up study, it was also found that the MRI findings were highly accurate when compared with histopathological analysis findings of the surgical specimens[18].

A reasonable hypothesis, corroborated by the findings of these earlier studies, is that the detection of confirmed additional disease on preoperative breast MRI to achieve radical surgery would decrease recurrence and mortality. Fisher *et al*. in 1986 had suggested that occult residual carcinoma is a relevant cause for tumour recurrence[19] and because local recurrence often leads to distant metastases, it is likely that eventually overall survival (OS) will decrease[20–25]. Nevertheless, the importance of occult lesions is questionable. Anatomical studies have shown that foci in the breast in quadrants away from the primary tumor have no impact on prognosis[26]. The Dutch breast cancer guidelines recommend treatment of focally positive margins after BCS in invasive tumors using only complementary whole breast irradiation including boost, thereby omitting re-excision[27].

No randomised studies have examined the long-term relationship between preoperative MRI, breast cancer recurrence, and survival. The purpose of this study is to report the 10-year follow-up of the POMB study with a focus on the long-term outcomes of disease-free survival (DFS) and OS.

METHODS

This randomised multicentre study was approved by the Ethical Board Committee in Stockholm and Uppsala (Dnr 2007/1057-31/4 and 2020-00351). The design of the POMB study has been previously described in detail[17]. It included 440 patients aged 56 years or less with newly diagnosed invasive and/or noninvasive clinical and screen-detected breast cancer regardless of the stage of disease and prognosis. Patients were randomised at three different breast cancer units to undergo preoperative breast MRI in addition to standard preoperative assessment (MRI group) or undergo only conventional imaging (control group). Two hundred and twenty patients were randomly assigned to each group. Patients excluded from the study were those with previous malignant disease in the ipsilateral breast, pregnancy/lactation, kidney disease, metal

implants, overweight and reduced mobility, claustrophobia, mental illness, or difficulties in comprehension of the study (*Figure 1*).

Information regarding patient demography, clinical data, tumour biology, histopathological tumour characteristics, surgical treatment, and neoadjuvant/adjuvant therapy was collected at the time of the initial POMB study and was supplemented between March and May 2020 when a review of all available recorded electronic charts was undertaken.

Adjuvant therapy was provided according to the national guidelines based on stage and prognostic markers. Patients treated with BCS or mastectomy with chemotherapy were followed annually using bilateral mammography, sonography, and clinical examination at the breast clinic or the department of oncology for the next 10 years to detect any locoregional and contralateral breast cancer recurrence or distant metastatic disease. Patients who had undergone only mastectomy were examined annually for 5 years. All patients were thereafter followed via the national mammography screening program, wherein women between 40 and 74 years of age are included. The presence, location, and extent of distant metastases were assessed using conventional chest radiography, computed tomography, or positron emission tomography/computed tomography in patients with locally advanced breast cancer.

Local recurrence was defined as any detected new invasive or in situ breast cancer limited to the ipsilateral breast or chest wall/mastectomy site previously affected by cancer after radiotherapy or at least 3 months after primary surgical treatment. Regional recurrence was defined as any ipsilateral malignancy detected in the axilla and/or in the supra/infraclavicular/internal mammary lymph nodes after adjuvant radiotherapy or 3 months after surgery. Distant metastases were recorded when metastatic cells or findings were detected outside regional lymph nodes, either by cytological/histological confirmation or after radiological assessment. Distant metastases detected before the date of surgery were regarded

as synchronous with the primary tumour and were not listed as an event. Contralateral breast cancer was defined as any breast cancer diagnosed in the untreated breast during the follow-up.

The follow-up time interval was calculated as the number of months from the date of randomisation to the date of death or emigration or the date of last known follow-up. For six patients in the MRI group, the date of randomisation was missing. For these patients, the date of diagnosis was used instead, because it most probably differed from the date of randomisation by only a few days.

DFS was defined as the time interval between the date of randomisation and the date of any breast cancer recurrence or death, even if the patients were not at risk for recurrence until the final surgery. OS was defined as the duration of time from randomisation to death from any cause. Breast cancer-specific survival was calculated similarly but included only deaths due to breast cancer.

Statistical analysis

The sample size in this study was based on a power calculation supported by data from a study by Bedrosian *et al*.[28] Patients accepting participation entered the original POMB trial by means of a telephone call to the randomisation center after disclosure of cancer diagnosis. A computer-generated algorithm was used for randomisation, and patients were randomly assigned on a 1:1 basis to the preoperative breast MRI group or the control group.

Kaplan–Meier plots were used to estimate and analyse the primary endpoint, DFS, as well as the secondary endpoint, OS, for each group. Log-rank tests were used for comparison. Cox regression analysis was used to estimate hazard ratios (HRs). All primary analyses were performed according to the intention-to-treat principle. A per-protocol analysis was performed excluding 10 patients from the MRI group who had not undergone MRI. They were added to

the controls. A subgroup analysis of patients with tumour stages I–III excluding those with more advanced disease was also performed.

All reported *P*-values were based on two-sided tests. *P*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software (version 26.0; IBM SPSS, Armonk, NY, USA).

RESULTS

Demographic data of the 440 included patients are presented in *Table 1* according to the randomisation group. The mean age of the patients was 46 years in each group and the median follow-up time for OS from randomisation until the end of the study was 10 years. Regarding survival, no patients were lost to follow-up, but two patients moved outside the study region, and the date of last screening was noted as the end of follow-up for DFS. There were only minor differences between the groups in terms of patient demography, clinical data, tumour biology, histopathological tumour characteristics, and neoadjuvant/adjuvant therapy.

Ten patients in the MRI group did not undergo MRI but all patients assigned to the MRI group were included following the intention-to-treat study plan[17,18]. Of the 440 women in the current analysis, 85.5 per cent and 80.0 per cent of the women in the MRI and control groups, respectively, were alive and free of cancer after 10 years (*Figure 2a*). The difference was not statistically significant ($P = 0.099$). The Cox regression analysis revealed that the risk of relapse or death was 46 per cent higher in the control group than in the MRI group (HR 1.46, 95% confidence interval [CI] 0.93–2.29).

Moreover, 90.9 per cent and 88.6 percent of women in the MRI and control groups respectively, were alive after 10 years ($P = 0.427$) (*Figure 2b*). The risk of death was 27 per cent higher in the control group than in the MRI group (HR 1.27, 95% CI 0.71–2.29). Breast cancer-specific survival data were similar to OS data, because only five patients died from other

causes. Data related to disease relapse are presented in *Table 2*. The control group was associated with a statistically significantly increased risk of any type of recurrence when combined compared to the MRI group, HR 1.64, 95% CI 1.004–2.670.

Per-protocol analysis for DFS and OS was performed after limiting the sample to all eligible patients, excluding 10 who did not undergo MRI and adding them to the controls (HR 1.40, 95% CI 0.89–2.20 and HR 1.16, 95% CI 0.65–2.09, respectively).

Because patients with more advanced disease were considered not likely to benefit from MRI, a subgroup analysis of patients without extensive spread of disease at diagnosis was performed. It showed that preoperative MRI resulted in a borderline statistically significant improvement in DFS when seven patients with stage IV disease were excluded (*P = 0.057*).

A separate sensitivity analysis for DFS was performed excluding two patients with previous breast cancer and three patients without confirmed breast cancer findings on histopathological analysis (HR 1.46, 95% CI 0.93–2.29). Results of the main analyses were qualitatively similar to the findings reported above.

In addition, analyses of DFS and OS were stratified according to breast cancer unit and the results were almost identical.

DISCUSSION

The use of MRI in the assessment of newly diagnosed breast cancer has been incorporated into clinical practice in resource-rich environments. It is being discussed whether detecting additional cancers using breast MRI and reducing re-excision rates yields any benefit for survival. The POMB study with its long and complete follow-up using a randomised population addressed a previously non-explored concern related to DFS and OS using preoperative breast MRI. After 10 years of follow-up, there was a slight, although nonsignificant, improvement in DFS and OS among women aged 56 years or younger with breast cancer randomised to undergo

breast MRI as an adjunct technique to standard preoperative assessment, especially in those without extensive disease.

The relative 10-year survival rate of women diagnosed with breast cancer was 86 per cent in 2016 according to the National Board of Health and Welfare[29]. However, prognosis tends to be poorer in younger patients with breast cancer. In this study, the OS rates were 90.9 per cent and 88.6 per cent for the MRI and control groups, respectively, which reflected adequate and efficient treatment.

In the present follow-up study, the reasons for the low number of contralateral breast cancer occurrences in the groups might have been the relatively small study population and an effect of adjuvant systemic therapy or hormonal therapy. These outcomes may also be reflected in the previous POMB study results[17], wherein MRI was found to be associated with a considerable number of contralateral and multifocal findings that would have remained undetected in the absence of preoperative MRI. Because of such findings, the surgical procedure and adjuvant therapy were adjusted for 20 per cent of patients in the MRI group. Thus, correct primary treatment could potentially be translated into improved long-term outcomes.

There are no other comparable randomised studies on preoperative breast MRI reporting survival data. Retrospective studies reported conflicting findings regarding breast cancer recurrence. In 2004, Fischer U *et al*.[30] compared 121 patients who underwent preoperative MRI with 225 patients who did not. The study demonstrated that preoperative MRI resulted in a statistically significant reduction in ipsilateral breast cancer recurrence rate (6.5 to 1.2 per cent) and a reduction in contralateral breast cancer rate (4.0 to 1.7 per cent) during 3 years of follow-up. The groups, however, showed a tendency to be unbalanced regarding patient age, risk of recurrence, and tumour size. Additionally, the recurrence rates were rather high during the short follow-up period. Another retrospective study by Solin *et al*.[31] compared an MRI group comprising 215 patients with a group of 541 women who did not undergo breast MRI. There

was no difference in the 8-year rate of any local recurrences or OS between the groups. Local recurrence rates of 3 and 4 per cent for patients who underwent preoperative breast MRI and those who did not, respectively, are rather low and demonstrating an improvement in such rates would be extremely difficult in a retrospective cohort study.

Sung *et al*. published a retrospective study that included 348 patients, and 50 per cent underwent preoperative MRI. In this group, there was a significantly increased proportion of patients with extremely dense breasts and mammographically occult tumours. More tumours in this group were synchronous and contralateral compared with those in the control group. The re-excision rate was lower in the MRI group, but no significant difference in locoregional recurrence or disease-free survival was observed[32].

Houssami *et al*.[33] investigated the potential association between preoperative MRI and breast cancer recurrence in an individual person data meta-analysis including 3169 women. They found that preoperative MRI was not associated with reduced risk of local and distant recurrences during 8 years of follow-up. However, some of the included studies did not have an optimal design and the results are difficult to interpret because the groups of patients are not directly comparable. In addition, as outlined by the authors, a longer follow-up duration could possibly show a trend toward a more obvious MRI-related benefit[33].

The current study has several strengths. It is a randomised study with a long follow-up. Because of the national security numbers in Sweden, no patients were lost to follow-up regarding survival. The MRI findings were evaluated by a few experienced specialists in radiology, and all of them were part of the diagnostic and therapeutic team. In this study, women aged 56 or less were selected, as they were more likely to have dense breasts, with the aim of including patients who would benefit the most from preoperative breast MRI.

While interpreting the results, it should be considered that only a few events occur even after a long-term follow-up, owing to the excellent prognosis of early-stage breast cancers. For

example, it is known that a small nonsignificant difference in survival between breast-conserving treatment with and without radiotherapy translates into a significant difference after 15 years of follow-up[34]. Whether this will also occur in the POMB cohort is still unknown, but it would indicate the need for a longer follow-up.

To date the most sensitive imaging modality for breast cancer detection is MRI. However, in terms of cancer specificity mammography is still superior. The continued development of imaging modalities has enabled the rise of contrast enhanced digital mammography (CESM) as an alternative with greater breast cancer specificity than MRI. CESM could therefore be of use for patients with contraindications to MRI as well as in regions with limited MRI availability[35]. However, whether improvement in diagnostic accuracy, leading to a more accurate primary surgery, generally extrapolates into a better prognosis, is still an unresolved issue.

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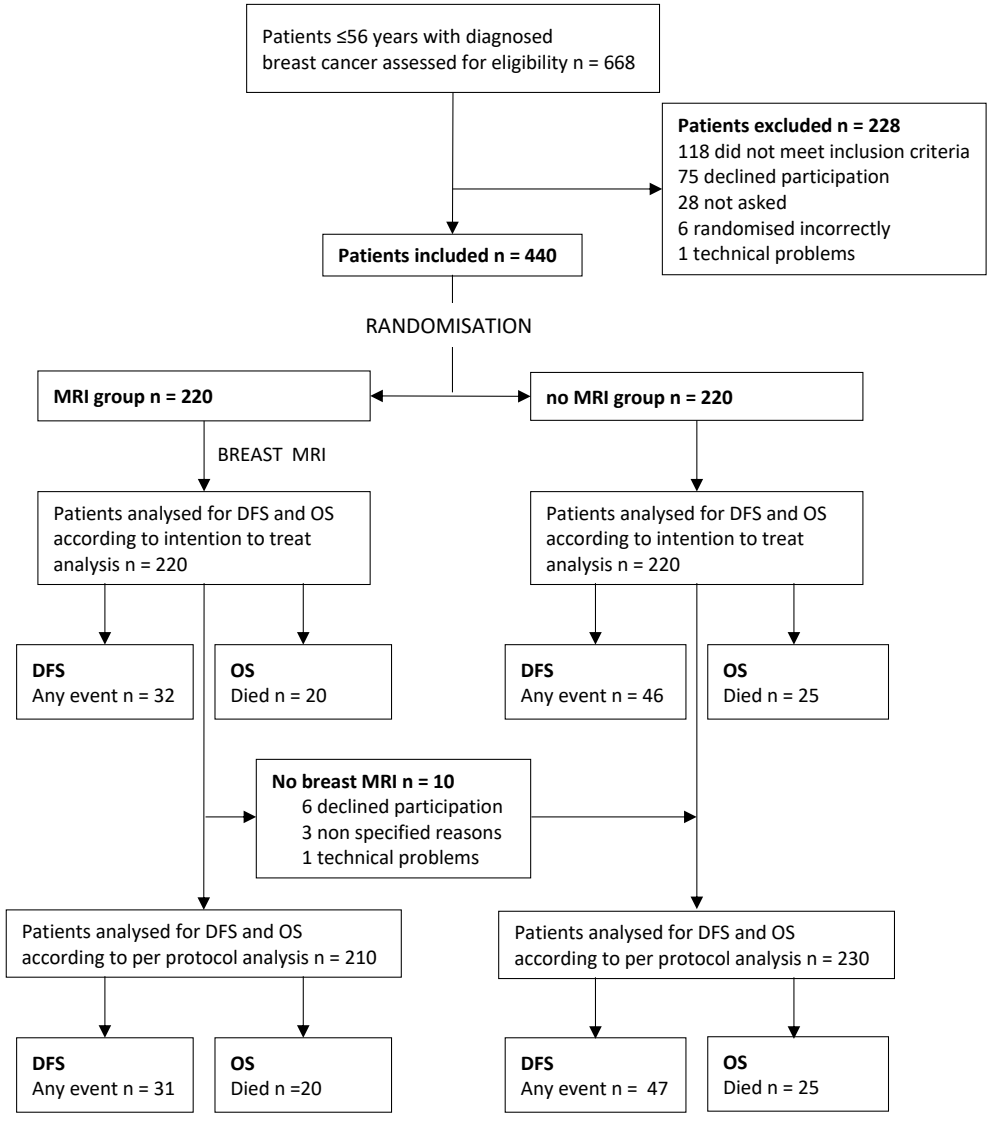
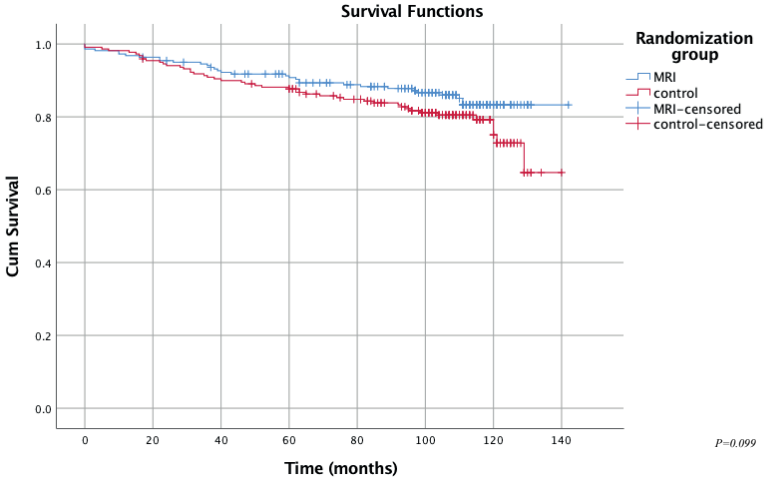
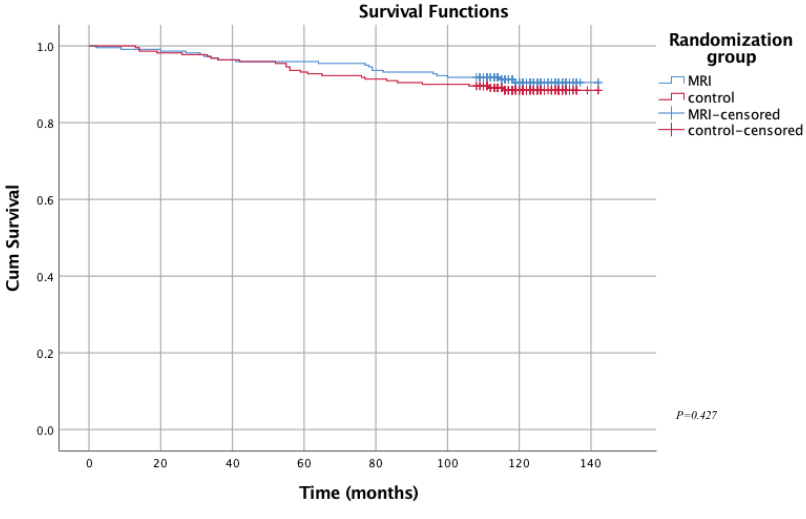


Fig. 1 Consort diagram



No. at risk							
MRI	211	203	200	195	192	188	188
Control	209	198	193	187	180	176	174

a.



No. at risk							
MRI	217	211	210	205	202	200	200
Control	215	211	204	200	197	195	195

b.

Fig. 2 Kaplan–Meier survival curves during 10 years of follow-up of 440 patients included in the POMB study with newly diagnosed breast cancer who did and did not undergo preoperative magnetic resonance imaging showing (a) breast cancer disease-free survival and (b) overall survival outcomes. Survival curves shown for intention to treat analysis.

Table 1. Patient demography, clinical data, tumour characteristics, and treatment of 440 patients included in the POMB study randomized to a preoperative magnetic resonance imaging group or a conventional imaging group.

	MRI (n = 220)			**Control** (n = 220)		
	n	**%**	**median/range**	**n**	**%**	**median/range**
Age at randomization (years)			46/27–55			46/21–56
Menopausal status						
Premenopausal	157	(74.4)		163	(74.1)	
Perimenopausal	28	(13.3)		26	(11.8)	
Postmenopausal	10	(4.7)		17	(7.7)	
Unknown	25	(7.6)		14	(6.4)	
Screen-detected breast cancer						
Yes	83	(37.7)		83	(37.7)	
No	137	(62.3)		137	(62.3)	
Breast density✤, dexter						
1	106	(48.2)		103	(46.8)	
2	85	(38.6)		83	(37.7)	
3	24	(10.9)		28	(12.7)	
4	5	(2.3)		5	(2.2)	
Unknown	0	(0.0)		1	(0.6)	
Breast density✤, sinister						
1	104	(47.3)		102	(46.4)	
2	85	(38.6)		85	(38.6)	
3	26	(11.8)		29	(13.2)	
4	5	(2.3)		4	(1.8)	
Tumour size						
Tis	19	(8.6)		25	(11.4)	
<2 cm	120	(54.5)		129	(58.6)	
>2 cm, <5 cm	62	(28.2)		45	(20.5)	
>5 cm	19	(8.6)		20	(9.1)	
Unknown	0	(0.0)		1	(0.5)	
Lymph node metastasis						
0	120	(54.5)		136	(61.8)	
1–3	69	(31.4)		65	(29.5)	
4–9	15	(6.8)		8	(3.6)	
>10	4	(1.8)		4	(1.8)	
Unknown	12★	(5.5)		7☆	(3.2)	
Type of invasive carcinoma						
Ductal	146	(66.4)		166	(75.5)	
Ductal and lobular	6	(2.7)		5	(2.3)	
Lobular	15	(6.8)		11	(5.0)	
Other	16	(7.3)		10	(4.5)	
Type of in situ carcinoma						
DCIS	108	(49.1)		129	(58.6)	
DCIS and LCIS	1	(0.5)		5	(2.3)	
LCIS	11	(5.0)		6	(2.7)	
Other	1	(0.5)		0	(0.0)	
ER* status						
Positive	162	(73.6)		158	(71.8)	
Negative	37	(16.8)		48	(21.8)	
Unknown	21	(9.6)		14	(6.4)	
PR* status						
Positive	149	(67.7)		146	(66.4)	
Negative	50	(22.7)		59	(26.8)	
Unknown	21	(9.1)		15	(6.9)	

HER2* status				
Positive	30	(13.6)	32	(14.5)
Negative	168	(76.4)	172	(78.2)
Unknown	22	(10.0)	16	(7.3)
	MRI (n = 220)		**Control** (n = 220)	
	n	**%**	**n**	**%**
Herceptin				
Yes	32	(14.5)	30	(13.6)
No	186	(84.5)	189	(85.9)
Unknown	2	(0.9)	1	(0.5)
Molecular subtype by proxy♣				
Luminal A	62	(28.2)	67	(30.5)
Luminal B HER2-	84	(38.2)	71	(32.3)
Luminal B HER2+	15	(6.8)	15	(6.8)
HER2+	11	(5.0)	17	(7.7)
Triple-negative	24	(10.9)	30	(13.6)
Unknown	24	(10.9)	20	(9.1)
Breast conserving surgery				
Yes	123	(55.9)	129	(58.6)
No	97	(44.1)	91	(41.4)
Radiotherapy				
Yes				
breast	73	(33.2)	78	(35.3)
locoregional	65	(29.5)	60	(27.3)
breast+boost	33	(15.0)	38	(17.3)
locoregional+boost	5	(2.3)	8	(3.6)
No	31	(14.1)	35	(15.9)
Unknown	13	(5.9)	1	(0.5)
Chemotherapy				
Yes	140	(63.6)	137	(62.2)
No	79	(35.9)	82	(37.3)
Unknown	1	(0.5)	1	(0.5)
Endocrine therapy				
Yes	160	(72.7)	153	(69.5)
No	59	(26.8)	66	(30.0)
Unknown	1	(0.5)	1	(0.5)
Chemo- and endocrine therapy				
Yes	104	(47.3)	93	(42.2)
No	115	(52.3)	126	(57.3)
Unknown	1	(0.5)	1	(0.5)

POMB study randomized to a preoperative magnetic resonance imaging group or a conventional imaging group.

✣Breast density according to American College of Radiology Breast Imaging Reporting and Data System: 1 = 0–25 % breast parenchyma, 2 = 25–50 % breast parenchyma, 3 = 50–75 % breast parenchyma, 4 = 75–100 % breast parenchyma

★Eight patients had no axillary surgery. ✲Four patients had no axillary surgery

*ER, Estrogen Receptor, PR, Progesterone Receptor, HER2, Human Epidermal Growth Factor Receptor 2

♣Luminal A (estrogen receptor (ER) positive and/or progesterone receptor (PR) positive, HER2-; Ki-67 <20%),
Luminal B HER2- (ER+ and/or PR+, HER2-; Ki-67 ≥20%),
Luminal B HER2+ (ER+ and/or PR+, HER2+; any Ki-67),
HER2 enriched (ER- and PR-, HER2+; any Ki-67),
Triple-negative (ER-, PR-, HER2-, any Ki-67)

Table 2. Disease recurrence and survival data after 10 years of follow-up of 440 patients included in the POMB study randomized to a preoperative magnetic resonance imaging group or a conventional imaging group. Hazard ratios indicate the risk of recurrence and death in the control group compared with that in the magnetic resonance imaging group.

	MRI (n = 220)		**Control** (n = 220)				
	n	%	n	%	*P*-value	HR	CI
Locoregional recurrence	13	(5.9)	19	(8.6)	0.275	1.482	0.732–3.000
Distant recurrence	16	(7.3)	26	(11.8)	0.116	1.647	0.884–3.071
Locoregional and distant recurrences	24	(10.9)	37	(16.8)	0.087	1.567	0.937–2.618
Contralateral recurrence	2	(0.9)	5	(2.3)			
Any recurrence	26	(11.8)	42	(19.1)	0.048	1.639	1.004–2.670
Any event (DFS*)	32	(14.5)	46	(20.9)	0.101	1.459	0.929–2.291
Death (OS*)	20	(9.1)	25	(11.4)	0.427	1.269	0.705–2.285
Breast cancer death (Breast cancer-specific survival)	17	(7.7)	23	(10.5)	0.321	1.373	0.734–2.570

DFS* = Disease free survival, OS* = Overall survival.