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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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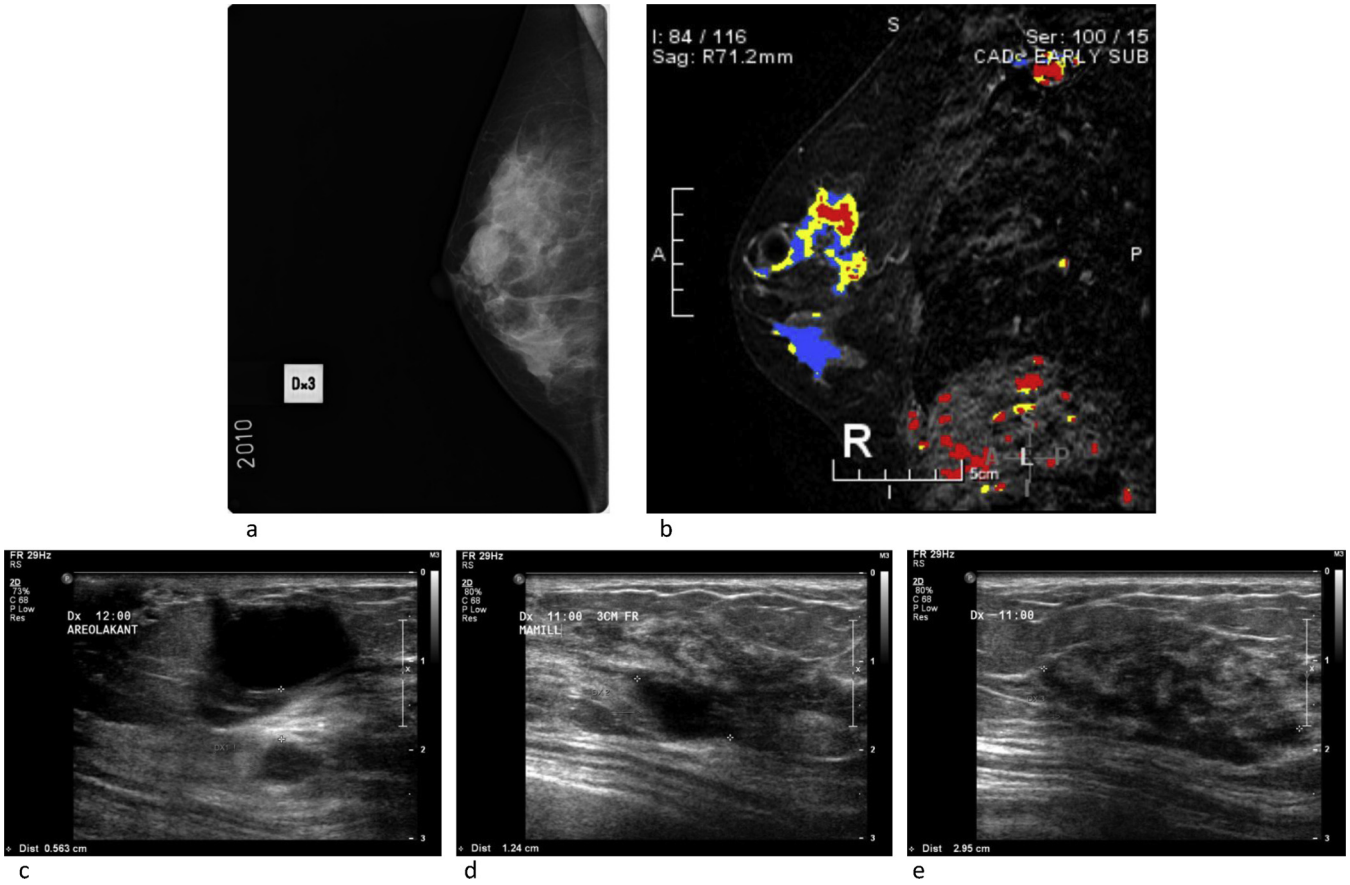

Fig. 1. Forty-one year old patient with a 25 mm large, palpable lump in the upper part of the right (Dx) breast. Initial mammography (a) and ultrasound (not shown) revealed a 23 x 12 mm cyst corresponding to the palpable finding. Cytology from the cyst fluid yielded cancer cells and the patient was randomized 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

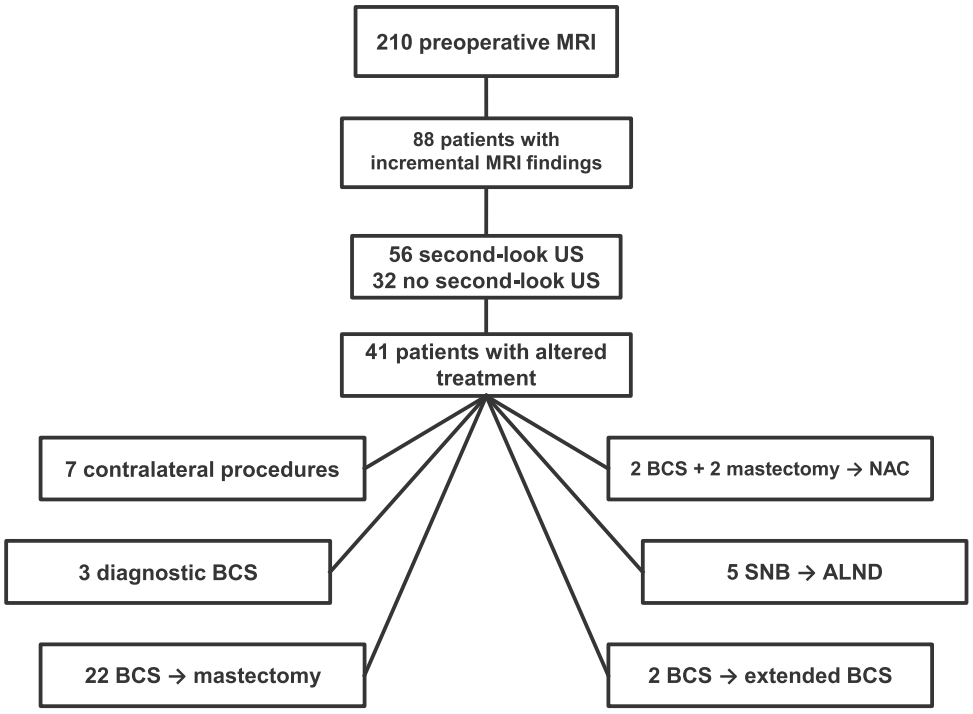

Fig. 2. Flow chart showing the number of MRI related additional diagnostic procedures and distribution of altered managements among 210 patients who underwent pre-operative breast MRI in the POMB trial.
Abbreviations; MRI = Magnetic Resonance Imaging, US = Ultrasound, BCS = Breast Conserving Surgery, 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.

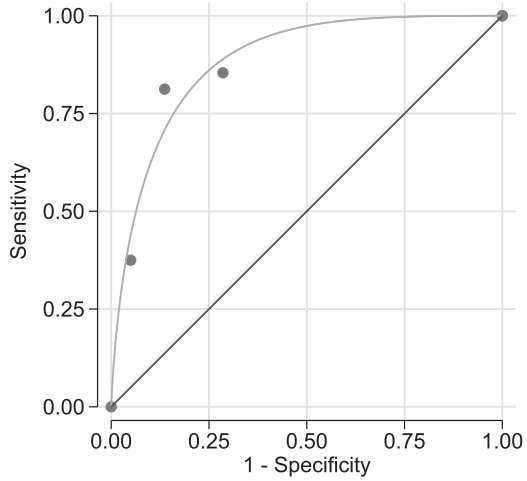

Fig. 3. Receiver Operating Characteristics curve and empiric data (dots) for the incremental findings in the MRI group in the POMB trial. Empiric AUC = 85% (95% CI 78–91%).

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.

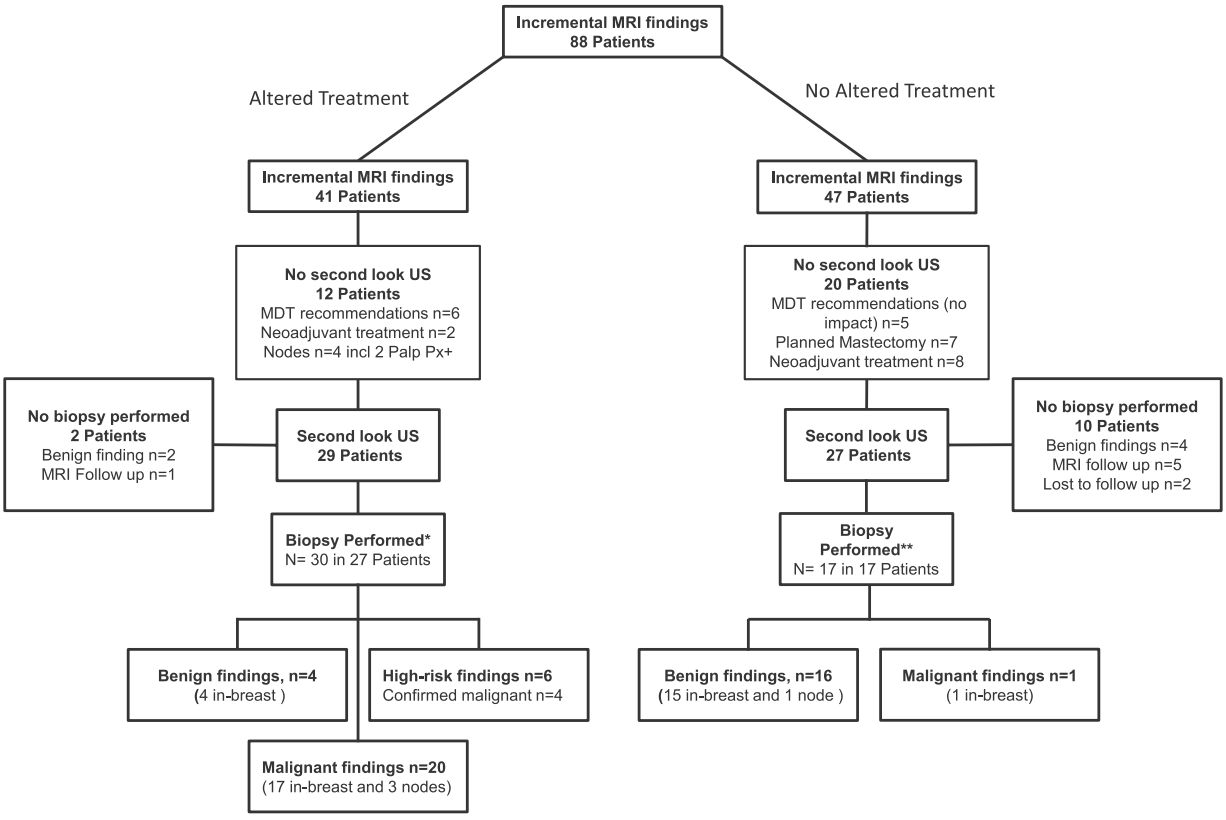

Fig. 4. Flow chart showing the number of patients with incremental findings who did and did not perform second-look US, number of biopsies and biopsy yields.
* Including one confirmed MRI guided biopsy.
** Including three benign MRI guided biopsies.

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Potential and real conflicts of interest

The authors declare no conflict of interest.

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