



**Preoperative Breast MRI in Clinical Practice:
Multicenter International Prospective Meta-Analysis (MIPA) of Individual Woman Data
An EIBIR-EuroAIM/EUSOBI Study**

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Study Outline

1. Background

Breast cancer remains a worldwide big killer with a rate of deaths compared with newly diagnosed cases not lower than 20% [1]. Many studies showed that breast conserving treatment, if compared with mastectomy, does not reduce survival rate implies a higher rate of ipsilateral recurrence [2]. Moreover, when a conserving surgical approach is used, positive or close margins at final histology require re-excision up to 20-40% of cases. A recent meta-analysis of 21 studies reported positive or close margins in 3,781 of 14,571 patients (26%); local recurrence odds ratio of 1.8 for close margins, 2.4 for positive margins, 2.0 for positive or close margins if compared to negative margins (odds ratio =1.0) ($P < 0.001$) [3]. In a large screening program, of 1,648 women who had conserving treatment, surgical margins were close (≤ 1 mm) or involved in 30% of cases and re-excision was performed in 17%, of whom 33% had residual disease identified [4]. In this context, bilateral contrast-enhanced breast MRI has been demonstrated to outperform mammography and ultrasonography in evaluating index tumor size as well as in detecting additional ipsilateral and contralateral tumors, showing otherwise undetected multifocal/multicentric and contralateral cancers. Meta-analyses showed a rate of 11% of patients with changed ipsilateral surgical treatment for MRI-detected additional cancers [5] and 3-4% of patients with MRI-detected contralateral cancers [6]. A recently published meta-analysis confirmed these data, showing similar percentages (12% and 3%, respectively) on a larger number of studies [7]. On the other side, false positives (implying the need of further assessment, including MR-guided biopsy) and overdiagnosis (i.e., the detection of cancers which would be cured with radiation therapy and/or systemic therapy) are possible. Notably, according to the recent meta-analysis [7], no information was available about the selection of patients in 15/50 studies (30%), a prospective design was reported only in 24/43 studies (56%), complete verification of MRI findings was obtained in 14/48 studies (29%), and MRI-guided procedures were available in 19/50 studies (38%). These methodological drawbacks highlight the need of data on the use of preoperative MRI from high-quality centers. Moreover, in some cancer centers an increased rate of mastectomies has been claimed as related with the use of preoperative MRI. Thus, preoperative MRI has become one of the most debated topics in breast cancer care literature. The EUSOMA working group recommended to limit the indications to particular patients subgroups (invasive lobular cancer; high-risk women; ≥ 1 -cm discrepancy in index tumor diameter between mammography and ultrasound; eligibility for partial breast irradiation) [8].

In this context, the results of two randomized controlled trials (RCTs) concerning preoperative MRI were recently published, none of them in favor of the use of preoperative breast MRI. The COMICE study [9] randomized over 1,600 women to conventional imaging plus MRI or conventional imaging alone for preoperative evaluation, reporting a not significant difference in re-excision rate for positive margins (19% in both arms). The MONET study [10] randomized to preoperative MRI or no preoperative MRI women with non palpable lesions, comparing 74 women with MRI versus 75 without MRI: the re-excision rate was significantly higher for the MRI group (34%) than for the non-MRI group (12%). The results of both RCTs were unexpected and have not definitively solved the clinical issue of using or not using MRI for a preoperative evaluation of breast cancer. In fact, several limitations and criticisms were raised against



both studies. The COMICE study was burdened by lack of experience with preoperative breast MRI, especially by surgeons, and lack of systematic use of MR-guided procedures. The MONET study suffered from a strong selection bias (50% of compared cancer cases were mammographically detected microcalcifications turned out to be DCIS). Both studies did not outline a strategy for translating MRI data to the operating theatre.

Notwithstanding these results and recommendations, preoperative breast MRI is increasingly used in clinical practice. In many centers a high-level cooperation between radiologists and surgeons, in the current context of increasing experience with breast MRI, may allow judicious and planned use of this tool, with a rate of treatment changed by MRI of about 10-12% [11, 12, 13].

Thus, a systematic evaluation of preoperative breast MRI looking at the individual patient data in a multicenter international setting could clarify the above matters regarding the ongoing uncertainty on application of preoperative MRI.

2. Aims/End-points

The aims of this study are defined as follows:

- I. To prospectively and systematically collect data on consecutive series of women with a newly diagnosed first breast cancer, not candidate to neoadjuvant chemotherapy, who undergo preoperative MRI (MRI group) or who do not (no-MRI group);
- II. To compare data on surgical outcomes for the MRI group with those obtained for the concurrent no-MRI group, matched for age (5-year age group strata), and if feasible histology (invasive ductal versus invasive lobular), and analytically adjusted for variables found to be significantly different between the two concurrent groups.

Primary end-point(s): proportion of patients receiving re-excision due to positive or close surgical margins in the two concurrent groups; overall rate of unilateral (or bilateral) mastectomy in the two concurrent groups.

Secondary surgical end-points:

- rate of change of surgical planning from that planned on basis of conventional imaging to that recommended on the basis of MRI findings in the MRI-group, overall and subdivided into: i) from unilateral mastectomy to unilateral BCS; ii) from unilateral BCS to unilateral wider BCS; iii) from unilateral BCS to unilateral mastectomy; iv) from unilateral BCS to bilateral BCS; v) other changes

Secondary non-surgical end-points:

- ipsilateral recurrence during 5-year follow-up;
- contralateral breast cancer during 5-year follow-up;
- diagnosis of distant metastases (confirmed by at least two imaging techniques) during 5-year follow-up.

3. Inclusion/exclusion

Inclusion (MRI group): women from 18 to 80 years of age with a newly diagnosed needle-biopsy proven first breast cancer.

Exclusion (MRI group): pregnancy; previous history of non-breast cancer at any site; previous history of breast cancer (invasive or DCIS); women candidates to neoadjuvant chemotherapy; women with evidence of distant metastases at the time of breast MRI; women with absolute contraindications to MRI or to gadolinium-based contrast materials according to international guidelines or local regulations (including $eGFR < 30 \text{ ml/min} \cdot 1.73 \text{ m}^2$); women who received any contrast material prior to breast MRI examination or are scheduled to receive any contrast material within 24 hours afterwards; mental disability precluding informed consent to participate.

Inclusion (no-MRI group): women from 18 to 80 years of age with a newly diagnosed needle-biopsy proven first breast cancer.



Exclusion (no-MRI group): pregnancy; previous history of non-breast cancer at any site; previous history of breast cancer (invasive or DCIS); women candidates to neoadjuvant chemotherapy; women with evidence of distant metastases at the time of conventional breast imaging (mammography/sonography); mental disability precluding informed consent to participate.

4. Sample size and statistical analysis

Assuming a baseline re-excision rate due to positive/close margins of 20%, we anticipate an absolute reduction from MRI of 5% (i.e., 15% re-excision for MRI-group versus 20% for non-MRI group). To detect this reduction at $P < 0.05$ and 90% power, we need a sample of 1,250 women in each group (total 2,500 women). At 80% power, we need a sample size of 946 per group (total 1,892 women). We would aim at about $1,300 \times 2 = 2,600$ women to allow for losses/missing data (220 patients per center \times 12 centers = 2,640 women). The two concurrent groups will be matched for age (5-year age group strata) and, if feasible, for histology (invasive ductal versus invasive lobular carcinomas), and analytically adjusted for other variables found to be significantly different between the two concurrent groups.

5. Selection of centers

The selection of the Centers will be done by the Steering Committee on the basis of the information supplied by the applicants answering the Call. Each center will be supported by the EIBIR with a grant 5,000 euros.

The following criteria will be taken into account:

- experience of the center in breast cancer care
- experience of the center with preoperative breast MRI
- experience of the center in second look sonography, US- and MR-guided procedures
- experience of local investigators in participating in breast cancer multicenter studies
- need to reach the study sample size for both MRI group and no-MRI group
- homogeneity of imaging protocols among the Centers, including MRI spatial and temporal resolution and type and dose of contrast agent
- scientific CV of local investigators

6. References

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