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Solving the preoperative breast MRI conundrum: design and protocol of the MIPA study

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Abstract

Despite its high diagnostic performance, the use of breast MRI in the preoperative setting is controversial. It has the potential for personalized surgical management in breast cancer patients, but two of three randomized controlled trials did not show results in favor of its introduction for assessing the disease extent before surgery. Meta-analyses showed a higher mastectomy rate in women undergoing preoperative MRI compared to those who do not. Nevertheless, preoperative breast MRI is increasingly used and a survey from the American Society of Breast Surgeons showed that 41% of respondents ask for it in daily practice. In this context, a large-scale observational multicenter international prospective analysis (MIPA study) was proposed under the guidance of the European Network for the Assessment of Imaging in Medicine (EuroAIM). The aims were (1) to prospectively and systematically collect data on consecutive women with a newly diagnosed breast cancer, not candidates for neoadjuvant therapy, who are offered or not offered breast MRI before surgery according to local practice; (2) to compare these two groups in terms of surgical and clinical endpoints, adjusting for covariates. The underlying hypotheses are that MRI does not cause additional mastectomies compared to conventional imaging, while reducing the reoperation rate in all or in subgroups of patients. Ninety-six centers applied to a web-based call; 36 were initially selected based on volume and quality standards; 27 were active for enrollment. On November 2018, the target of 7000 enrolled patients was reached. The MIPA study is presently at the analytic phase.

Key Points

- *Breast MRI has a high diagnostic performance but its utility in the preoperative setting is controversial.*
- *A large-scale observational multicenter prospective study was launched to compare women receiving with those not receiving preoperative MRI.*
- *Twenty-seven centers enrolled more than 7000 patients. The study is presently at the analytic phase.*

Keywords Breast neoplasms · Breast-conserving surgery · Magnetic resonance imaging · Mastectomy · Prospective studies

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Abbreviations

BCS	Breast-conserving surgery
EuroAIM	European Network for the Assessment of Imaging in Medicine
EUSOBI	European Society of Breast Imaging
MRI	Magnetic resonance imaging
OR	Odds ratio
RCT	Randomized controlled trial

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Introduction

Breast-conserving surgery (BCS) with whole breast irradiation is the best option for operable breast cancers, comparable to mastectomy in terms of survival [1, 2], with generally better psychosocial outcomes. However, after BCS, the risk of locoregional recurrences or new ipsilateral/contralateral cancers is 1.0 to 1.5% per year for 15–20 years [3]. In addition, the rate of positive/close margins after BCS is 26–30% [4, 5] usually leading to reoperation.

The role of preoperative contrast-enhanced breast MRI emerged in this surgical context. It showed an unparalleled sensitivity in comparison with mammography and/or ultrasound [6–12]. When compared to double-reading mammography in 99 mastectomies [13], its sensitivity (81%) was significantly higher than that of mammography (66%). A large study [14] reported over 95% sensitivity and specificity while another study [15] reported that 23% of MRI-detected additional tumors were larger and 5% more biologically important than the index cancer. In meta-analyses, the frequency of MRI-detected additional cancers was around 20% [16], in agreement with the high rate of multifocal/multicentric cancers found at pathology of mastectomy specimens [17], while the rate of additional contralateral cancers was 4–5% [16, 18].

Breast MRI has been advocated to personalize the surgical management, reducing reoperation rate and early-detecting contralateral cancers, with a potential for improving disease-free survival. However, two of three randomized controlled trials (RCT) [19, 20] did not confirm better surgical outcomes, and the third [21], focusing on relatively younger women was in favor of MRI. Furthermore, a recent RCT of 360 patients with ductal carcinoma in situ failed to show a significant reduction of the reoperation rate in the MRI group over the control group (20% versus 27%) highlighting the need for large sample sizes to examine benefits in subgroups [22].

A meta-analysis [23] found a first-line mastectomy rate significantly higher for the MRI group (16%) than for the no-MRI group (8%), a similar reoperation rate (12% versus 11%, respectively), and an overall (first-line plus secondary) mastectomy rate significantly higher for the MRI group (26% versus 18%, respectively). In patients with invasive lobular histology, the first-line mastectomy rate was 31% versus 25%, the reoperation rate 11% versus 18%, and the overall mastectomy rate 43% versus 40%, respectively (with significance borderline or dependent on adjustments).

An individual patient data meta-analysis [24] showed that the 8-year local and distant recurrence-free survival did not significantly differ between patients locally staged with or without MRI. Another meta-analysis [25] did not find evidence that MRI improved surgical outcomes while the odds for ipsilateral mastectomy (odds ratio [OR] 1.39) and contralateral prophylactic mastectomy (OR 1.91) were significantly increased. In the subgroup of invasive lobular histology, MRI was not associated with an increase in mastectomy rate (OR 1.0) but with a reduced probability of reoperation (OR 0.65), although not at statistically significant levels.

Data from these studies are summarized in Table 1.

The discussion regarding the utility of preoperative MRI has not ended yet, with arguments in favor [26, 27] and against [28–30], and remains an unsolved aspect of breast cancer management [31, 32]. While MRI certainly improves disease extent definition, there is conflicting evidence and uncertainty on whether and in whom it is beneficial, underscoring the need for additional evidence.

The American Society of Breast Surgeons [33] suggests "*Don't routinely order breast MRI in new breast cancer patients*." However, regardless of evidence and recommendations, a survey from that society [34] showed that 41% of responding surgeons use preoperative MRI in daily practice. Another survey [35] showed a surgeons' propensity for requesting MRI in case of (in decreasing order) *BRCA* mutations; familial/personal breast cancer history; dense breasts; age < 40; axillary nodal involvement; mammographically occult tumor; multifocal/multicentric disease at conventional imaging; invasive lobular histology; triple-negative cancer; T2–T3 stage; candidates for mastectomy requesting breast-conserving surgery (BCS); and radiologist's discretion.

A prospective multicenter trial to solve the conundrum

An international group (European Network for the Assessment of Imaging in Medicine, EuroAIM; https://www.eibir.org/initiatives/euroaim/) established a collaborative plan to conduct a large-scale observational multicenter international prospective analysis (MIPA) study to be performed in institutions providing high-volume breast MRI and high-quality standards. The aims were (1) to prospectively and systematically collect data on consecutive women with a newly diagnosed first breast cancer, who are not candidates to neoadjuvant therapy, and who are offered MRI (MRI group) or not (no-MRI group) as part of local breast cancer management; (2) to compare these two groups in terms of characteristics, and surgical and clinical endpoints. The underlying hypotheses are that MRI does not cause additional mastectomies compared to conventional imaging, while reducing the reoperation rate in all or subgroups of patients.

International open call

The MIPA study was undertaken under the initiative and responsibility of the EuroAIM and endorsed by the European Society of Breast Imaging (EUSOBI). Bayer Healthcare provided an unconditional research grant for the conduct of the study.

Table 1 Summary of comparative studies on preoperative breast MRI

Article	Design	Population	MRI (N.)	No MRI (N.)	First-line mastectomy		Reoperation rate*		Remarks
					MRI	No MRI	MRI	No MRI	
Turnbull 2010 (COMICE) [19]	RCT	Cancer patients scheduled for BCS	816	807	7%	1%	19%	19%	Per-patient analysis. OR for reoperation within 6 months 0.96 ($p = 0.77$). Patients scheduled for mastectomy before MRI were excluded.
Peters 2011 (MONET) [20]	RCT	Patients with non-palpable suspicious lesions (BIRADS 3, 4, or 5)	74	75	32%	34%	23%	6%	Per-breast analysis. p value for reoperation 0.008. Non-cancer patients were excluded from this table.
Gonzalez 2014 (POMB) [21]	RCT	Cancer patients aged < 56, including candidate to NAT	191	192	31%	27%	6%	17%	Patients undergoing to NAT were excluded from this table. Suggested mastectomy rate before MRI was lower in the MRI group than in no-MRI group (18% versus 23%)
Balleyguier 2019 (IRCIS) [22]	RCT	Patients with pure DCIS	178	174	18%	17%	20%	27%	Per-patient, per-protocol analysis. OR for reoperation 0.59 ($p = 0.05$)
Houssami 2013 [23]	SR + MA	Studies with only pure DCIS were excluded	1802†	2408†	16%	8%	For wide local excision, 12% Converted from BCS to mastectomy 6%	For wide local excision, 11% Converted from BCS to mastectomy 7%	Adjusted OR for first-line mastectomy (1193 versus 1505; 4 studies) 3.06 ($p < 0.001$). Adjusted OR for reoperation for wide local excision (1261 versus 1736; 6 studies) 0.95 ($p = 0.71$). Adjusted OR for conversion from BCS to mastectomy (1009 versus 1251; 4 studies) 0.76 ($p = 0.12$). Reoperation rates were calculated over the number of patients undergoing BCS.
Houssami 2014 [24]	IPD MA	Breast cancer patients	1833	1347	15%	8%	–	–	HR for first-line mastectomy 0.80 ($p = 0.75$). Eight-year local recurrence-free survival did not differ between the MRI (97%) and no-MRI (95%) groups ($p = 0.87$).
Houssami 2017 [25]	SR + MA	Studies with only pure DCIS were excluded. All but one study excluded candidates to NAT. Two studies excluded patients with BRCA gene mutations.	15,274	70,701	–	–	Restricted to BCS, 10.9%	Restricted to BCS, 8.6%	OR for first-line mastectomy 1.39 ($p < 0.001$). OR for reoperation after BCS 1.19 (CI 0.89–1.66) ($p = 0.316$). OR for contralateral prophylactic mastectomy 1.91 ($p = 0.003$)

*Unless otherwise specified, proportion was recalculated by us as number of reoperations over the whole study population when reported over the number of patients undergoing BCS

†Based on all studies analyzed in this meta-analysis including studies restricted to invasive lobular cancer

BCS breast-conserving surgery, *DCIS* ductal carcinoma in situ, *HR* hazard ratio, *IPD* individual patient data, *MA* meta-analysis, *MRI* magnetic resonance imaging, *NAT* neoadjuvant therapy, *OR* odds ratio, *RCT* randomized controlled trial, *SR* systematic review

In mid-2012, an open call was published on the EuroAIM website and circulated within the EUSOBI members. Applying centers had to confirm a series of preliminary conditions pertaining to quality of MRI, focusing on equipment and workload (Table 1 of Supplemental material). Moreover, they had to anticipate (1) the approximate number of patients potentially recruitable; and (2) the local rate of MRI performed in women newly diagnosed with breast cancer.

Once selected, centers provided technical details of the MRI protocols applied locally. The coordinating center approved only MRI protocols following technical recommendations issued by international societies such us the European Society of Breast Cancer Specialists (EUSOMA) [36], the EUSOBI [37], and the American College of Radiology [38]. Details are shown in Table 2.

Study design and population

MIPA is a multicenter observational prospective study enrolling women newly diagnosed with breast cancer. No experimental intervention was planned. Centers were free to perform or not perform MRI according to local practice. Thus, two concurrent groups resulted *ex post* by whether women underwent preoperative staging using conventional imaging only (no-MRI group) or also received contrast-enhanced MRI (MRI group) in addition to conventional imaging, representing real-world breast cancer management (study registration ISRCTN41143178).

The study was conducted in accordance with the Declaration of Helsinki and was firstly approved on January 29, 2013, by the ethics committee at the coordinating center (protocol number 2784). Thereafter, ethical approval was obtained at each center. All participants signed an informed consent allowing the use of their data according the observational design.

The coordinating center at the Research Hospital (IRCCS) Policlinico San Donato (San Donato Milanese, Milan, Italy) was charged to ensure that the research data were accurate, complete, and consistent. The description of the database set up is reported in the supplemental material.

The study population included women aged 18 to 80 years newly diagnosed with a first breast cancer amenable to upfront surgery. Exclusion criteria included indication to neoadjuvant therapy, pregnancy, personal history of invasive or ductal in situ breast cancer, personal history of any cancer, evidence of distant metastases at enrollment, and inability to provide informed consent. Women with contraindications to MRI or to gadolinium-based contrast agents were included in the no-MRI group. The study flowchart is shown in Fig. 1.

Table 2 Preoperative breast MRI: technical requirements and imaging protocols of the MIPA study

Technical requirements	
Magnetic field strength	≥ 1.5 T
Gradients power	≥ 20 mT/m
Channels of dedicated coil	≥ 4
Technical protocol	
One of the following T2-weighted sequences (axial or sagittal):	
– Fast/turbo spin-echo ± fat-sat	
– Short tau inversion recovery (STIR)	
– Spectral pre-saturation with inversion recovery (SPIR)	
Contrast agent type and dose: extracellular gadolinium-based contrast agent, 0.1 mmol/kg	
Dynamic study (2D or 3D T1-weighted gradient-echo sequence ± fat-saturation, axial or sagittal)	
– Slice thickness ≤ 3 mm	
– In-plane resolution ≤ 1.5 mm^2 (preferably ≤ 1 mm^2)	
– Temporal resolution ≤ 120 s	

2D two-dimensional, *3D* three-dimensional

Study endpoints and statistical analysis

Primary surgical endpoints for the two groups are (1) the rate of mastectomies actually performed; and (2) the reoperation rate for close or positive margins among patients undergoing BCS. A secondary surgical endpoint for the MRI group only is the rate of change, after MRI, to more extended unilateral BCS (wider excision or multiple excisions) or to less extended BCS, or from unilateral BCS to bilateral BCS or vice versa. Secondary clinical endpoints for the two groups are the rate of (1) ipsilateral recurrences, (2) contralateral breast cancers, and (3) distant metastases at 5-year follow-up.

Assuming a reoperation rate due to positive/close margins in the no-MRI group of 20%, we anticipated a reoperation rate in the MRI group of 15%. To detect this reduction with an α error of 0.05 and 90% statistical power, 1250 women in each group (total 2500 women) should have been enrolled. To allow for 10% losses/missing data during follow-up, 1400 × 2 = 2800 women would have been needed. As the primary endpoint (reoperation rate) will be compared also in the subgroup of patients with ductal carcinoma in situ, which represents about 20–25% of all breast cancers [39, 40], the target sample size was set at 7000 patients to support subgroup analyses. Considering the large dataset, the sample size will allow explorative analyses for further hypotheses including other histology subgroups (e.g., lobular).

The two concurrent groups will be initially compared in terms of baseline characteristics such as demographics and breast density. As both groups receive conventional imaging, baseline characteristics include the surgical plan based on conventional imaging only, as defined by the multidisciplinary team or through direct interaction between radiologists and surgeons. As this is an observational study, this comparison can provide an insight on criteria used by physicians when ordering preoperative breast MRI that might cause selection

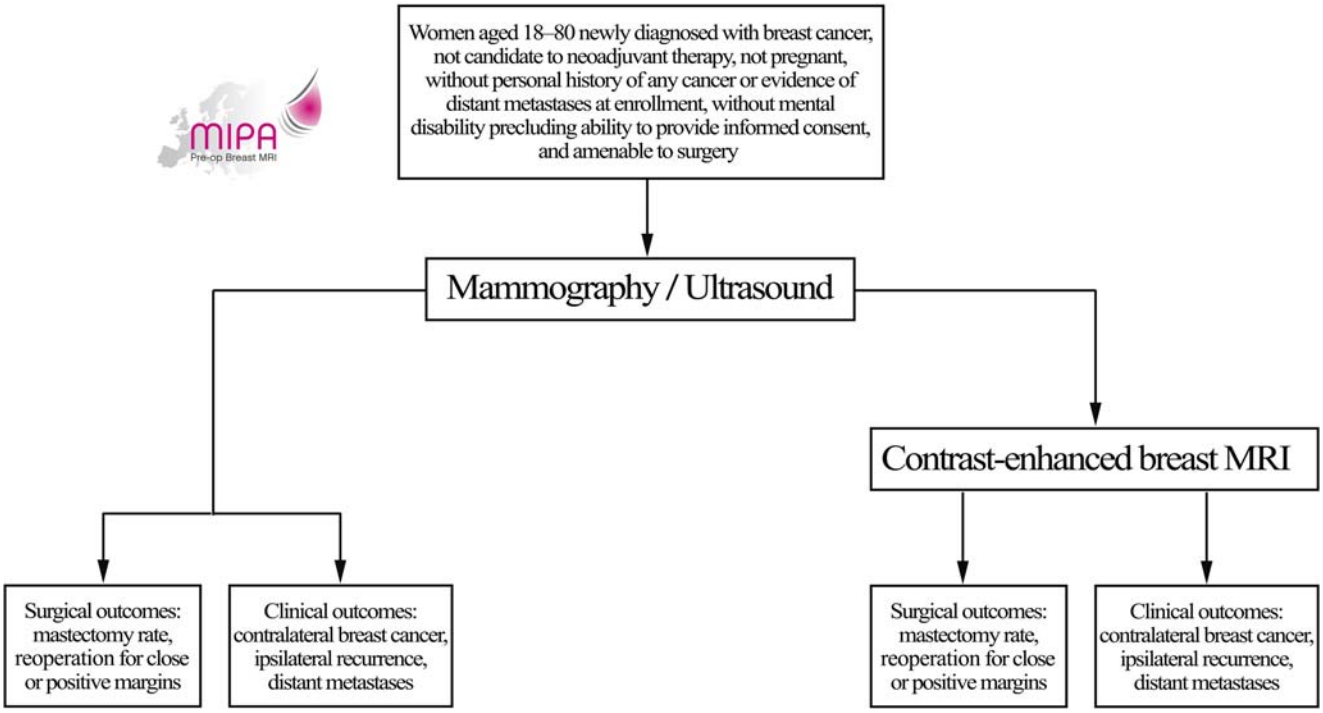

Fig. 1 Flowchart of the prospective observational multicentre MIPA study. Allocation to MRI was based on local clinical practice

biases. To this aim, the odds ratio (OR) of plan for mastectomy after conventional imaging will be calculated for the MRI group relative to the no-MRI group.

Depending on distributions, comparisons of continuous variables will be carried out using Student *t* test or Mann-Whitney *U* test for independent data, and using χ^2 test for categorical variables. Variables that will be shown to be significantly different between the two groups will be considered as covariates when the two groups will be compared in analyses.

For the primary endpoints, statistical analysis will be performed on a per-patient basis. The two concurrent groups will be compared by calculating the OR for mastectomy for the MRI group over the no-MRI group, raw and adjusted for covariates. A similar analysis will be carried out for the reoperation rate in patients undergoing BCS. Moreover, as in a before-after intra-individual study design, the rate of mastectomy before and after MRI in the MRI group will be compared using the McNemar test for paired data. Hence, changes of treatment planning from BCS based on conventional imaging as well as on available clinical examination and pathological data to mastectomy after MRI may compensate for the opposite change.

For secondary surgical endpoints regarding the MRI group only, per-breast distributions will be calculated using the same methodology described above for primary endpoints. Conversely, secondary clinical endpoints will be determined on a per-patient basis. Further analyses will be performed, including investigation of homogeneity across centers and temporal trends for both primary and secondary endpoints.

Timeline

In about 2 months following the open call, a total of 96 centers applied from all over the world. Thirty-six centers were initially selected based on pre-defined criteria: (1) the full respect of quality standards requested by the call (see Table 1 of Supplemental material); (2) the anticipated total number of patients that could potentially be enrolled in the center; and (3) the anticipated rate of patients that usually undergo preoperative MRI at the center. This allowed careful selection of centers among those with the highest volumes of breast MRI whilst also ensuring to balance the expected rate of MRI at about 50%.

After the study had begun, nine centers abandoned the study or never enrolled patients, four centers started the enrollment with very few patients but did not provide valid data; four centers were added later to replace the vacancies, so 27 centers were actively enrolling. The list of the 27 active centers is shown in Table 3.

During the pilot procedure run, few concerns were raised from local investigators and were fixed promptly. Valuable input came from centers for a further refinement of the electronic case report form, in particular, due to wording that was potentially misleading. The first woman was enrolled in June 2013. On November 30, 2018, the target of 7000 enrolled breast cancer patients was reached. The distribution of patients enrolled in each participating center is shown in Table 3. The enrolment is ended, while the follow-up should end by November 2023. Data cleaning and statistical analysis

Table 3 List of the 27 centers participating in the MIPA study and number of enrolled patients

Center	Enrolled patients
Radboud University Medical Center, Nijmegen, The Netherlands	956
Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine, Italy	619
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy	504
University of Cambridge, Addenbrooke's Hospital, Cambridge, UK	485
Hospital Universitario Reina Sofia, Cordoba, Spain	439
Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey	400
Medical University of Vienna, Vienna, Austria	368
Sociedade Beneficente De Senhoras, Hospital Sirio Libanes, Sao Paulo, Brazil	301
Maastricht University Medical Center, Maastricht, The Netherlands	265
IEO, Istituto Europeo di Oncologia, Milan, Italy	248
Radiologic Institute University, Erlangen, Germany	246
University Hospital, Tübingen, Germany	244
IRCCS Azienda Ospedaliera Universitaria San Martino, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy	233
Antwerp University Hospital, Antwerp, Belgium	228
Maatschap Radiologie Oost-Nederland, Oldenzaal, The Netherlands	207
Institut de cancérologie Gustave-Roussy	195
Sapienza University, Policlinico Umberto I, Rome, Italy	191
Erasmus Medical Center, University Hospital Rotterdam, Rotterdam, The Netherlands	178
Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy	166
The Breast Center of Northwest Arkansas, Fayetteville, USA	142
Central Military Hospital, Budapest, Hungary	132
IRCCS Ospedale San Raffaele, Milan, Italy	113
Hospital de la Ribera, Alzira, Spain	95
Royal Perth Hospital, Perth, Australia	66
University Hospital, Münster, Germany	66
Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, Italy	40
BHR Hospitals NHS Trust, Romford, UK	27
Total	7154

The study was coordinated by the Research Hospital (IRCCS) Policlinico San Donato, San Donato Milanese, Milan, Italy

of the baseline data is being conducted and the first paper with the main results will be submitted by 2020.

Conclusion

The use of preoperative MRI of the breast is controversial, mainly because it can affect the surgical planning and yet the evidence on its effect and clinical benefit has been discordant. The MRI diagnosis of additional cancers can change a BCS into mastectomy also when those lesions would be successfully treated by whole breast irradiation and/or systemic therapy, working against reducing surgical aggressiveness.

In the first years of breast MRI, the variable reported specificity [41, 42] combined with a limited use of target ultrasound and the lack of MRI-guidance for biopsy/localization also made MRI false-positives difficult to manage [19]. To transfer knowledge about disease extent demonstrated by MRI, performed in the prone position, to the surgical theater with the patient in supine position, is not easy [43]. A learning curve gradually improved the performance of radiologists in using targeted ultrasound [44], second-look mammography/tomosynthesis [45], and MRI-guidance [46]. Surgeons as well needed time to learn how to exploit the additional information from preoperative breast MRI.

The application of evidence-based medicine [47] is difficult in this setting. Preoperative MRI joins three clinical issues: (1) measuring the size of the index lesion; (2) searching for ipsilateral additional cancers; and (3) screening for contralateral cancers. While the first requires cohort studies correlating sizes at MRI and histopathology, the third is a screening-like task, theoretically needing RCTs before implementation [47, 48]; the second issue is arguably in the middle. Considering the treatments still prevalent for breast cancer

including whole breast irradiation following BCS, mastectomy for multicentric cancers, and variable systemic therapy, effects of preoperative MRI are difficult to assess.

The strength of the MIPA study is its special design. In fact, two designs were combined to derive the highest evidence possible: a case-control approach allowing the comparison of women undergoing MRI and women not undergoing MRI, and a before-after approach to have a direct measure of the MRI impact on surgery. The well-known limitations of the case-control approach will, in turn, result in an advantage for the MIPA study. In fact, whatever the difference between the two groups in terms of mastectomy/reoperation rate, the knowledge of the treatment plan after conventional imaging even in the MRI group will provide evidence on possible selection bias. From the other side, the before-after approach will allow not only the estimation of the additional mastectomy rate independently prompted by MRI (that may also be negative, meaning that MRI reduces the mastectomy rate) but also the evaluation of the changes of surgical extension in those women undergoing BCS, from less extensive to more extensive and vice versa.

Although the lack of randomization is a limitation of the MIPA study, it can be considered an effective and pragmatic way to provide evidence that is closer to the *real-world* approach [49, 50]. Especially from the intra-individual part of the study (comparing the plan for mastectomy before and after MRI), we will provide a clear insight into MRI's impact on patients' surgical management. Moreover, thanks to large number of patients and data that were collected, we will be able to answer several other questions. In particular, subgroup analyses will ascertain which patients will benefit the most from preoperative MRI. Correlation analyses will instead clarify the role of potential predictors, while follow-up data will provide evidence on cancer recurrences.

In conclusion, a large-scale real-world prospective multicenter study investigating the role and effect of MRI in the preoperative setting was launched internationally. This exemplar of the joint efforts of 27 centers enabled the target of 7000 women with newly diagnosed breast cancer to be reached and the study is presently at the analytic phase.

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Compliance with ethical standards

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Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- observational
- multicenter study

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