The European Experience with Multi-Center Breast MR Trials

Francesco Sardanelli, M.D.
European Network of Assessment of Imaging in Medicine (EuroAIM)
Department of Biomedical Sciences for Health, University of Milan School of Medicine
Radiology Unit, IRCCS Policlinico San Donato, Milan, Italy
(francesco.sardanelli@unimi.it)

In the last twenty years MR entered clinical practice in the field of breast imaging, where well-established imaging techniques played a key role for both screening and diagnostic imaging. MR had to highly compete with mammography, which became available on a digital platform including tomosynthesis, and ultrasonography (US), allowing also for contrast-enhanced studies and evolving into automated breast US. Moreover, in the case of a suspected cancer, we are able to easily sample a breast lesion using a needle under mammography (stereotactic) or US guidance. Notwithstanding this apparent closed pathway, breast MR managed to gain an acknowledged role in a series of indications including high-risk screening, prediction and evaluation of response to neoadjuvant chemotherapy, evaluation of patients with breast augmentation or reconstruction; occult primary breast cancer [1]. While new indications are emerging, such as evaluation of lesions with uncertain malignant potential at needle biopsy [2] and nipple discharge [3], preoperative breast MR remains a debated topic due to the risk of overdiagnosis and overtreatment [1, 4, 5]. Looking for high levels of evidence, not only in terms of technical or diagnostic performance but in terms of diagnostic/therapeutic impact and of patient outcome is mandatory, especially in an oncologic field where screening mammography was acknowledged as providing a societal effect in reducing breast cancer mortality.

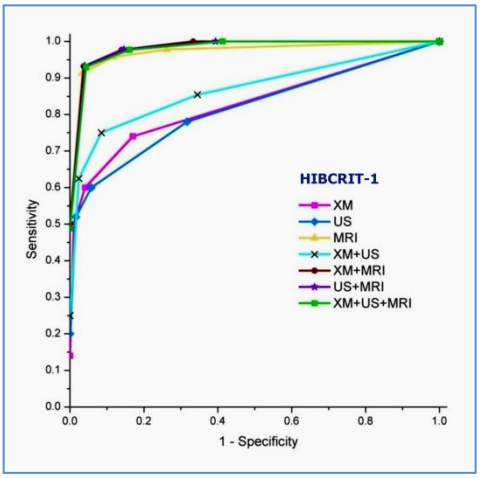
Multicenter trials should be considered as the most powerful tool for investigate the value of any new health technology, providing results which try to shift from efficacy to effectiveness on a large scale, overcoming the intrinsic limitations and potential biases of single-center studies. In Europe, breast MR has been evaluated on the benchmark of multicenter studies from 1997 to 2012, with results reported in 48 published papers, involving over 11,000 different patients. Taking in consideration the number of the papers, this European experience was mainly based in UK (n=15), Italy (n=8), The Netherlands (n=6), and Germany (n=4). These reports were published more frequently in clinical or non-radiological/imaging journals (n= 26; 54%) than in radiological/imaging journal (n=22;46%), the former mainly being oncologic or general medical journals, showing the impact of breast MR multicenter research on the entire medical community. These results concern the following topics: screening of women at increased risk of breast cancer (n=24; 50%); diagnostic performance and contrast materials (n=11; 23%); MR guided procedures (n=4; 8%); preoperative MRI (n=3; 6%); other (n=6; 13%).

The large majority of the reports on screening of women at increased risk of breast cancer comes from five relevant studies: MRISC, The Netherlands [6]; MARIBS, UK [7]; EVA, Germany [8]; HIBCRIT-1, Italy [9]; and one study from Norway [10]. The common results of all these studies is that breast MR outperforms mammography for early diagnosis of breast cancer in women at increased risk. These European studies largely contributed to the body of evidence in favor of the use of breast MR for screening high-risk women [11-15]. Notably, two recent studies, the EVA and the HIBCRIT-1, demonstrated that adding mammography and/or US (even if the latter is performed every six months) does not add diagnostic power, as it is shown at ROC analysis for the HIBCRIT-1 study (see Figure), opening a perspective for an MR-only screening of women at high-risk of breast cancer.

An important consequence of the multicenter setting of all these studies is a progressive standardization of high-quality breast MR protocols across European countries, including dynamic studies with power-injected 0.1 mmol/kg of contrast material and high in-plane spatial resolution (up to pixel size lower than 1 mm square), reasonably compensated by a temporal resolution up to 120 seconds [1, 15].

An important contribution to standardization came from the U.S. The extension to MRI of BI-RADS [16] lexicon and diagnostic categories allowed for a great advance in terms of reproducibility of breast MR description and interpretation, providing a clear message to clinicians. Comparisons across studies and individual patient data meta-analysis were also facilitated by the worldwide use of the MRI BI-RADS.

Multicenter studies are the main street for generating evidence in favor of breast MRI. This is true also for preoperative MRI. One large multicenter randomized controlled trial, the COMICE study [17], burdened by a series of problems and limitations, did not show any advantage of MRI in this setting. A new study (the MIPA project, coordinated by the European Institute for Biomedical Imaging and Research/EuroAIM), including 36 centers (30 of them from Europe), is now ongoing with the aim of comparing surgical and long-term outcomes of two very large concurrent cohorts of women receiving or not receiving preoperative breast MRI [18].



ROC analysis of diagnostic performance of mammography (XM), ultrasonography (US), and MRI for 1,592 screening events in 501 high-risk women (HIBCRIT-1 study, ref. #9). During the study 52 breast cancers, 48 screen-detected and 3 interval cancers were found. No significant differences in the area under the curve were observed between MRI alone and MRI plus XM) and/or US.

References: [1] Sardanelli et al, Eur J Cancer 2010; [2] Londero et al, AJR 2012; [3] Lorenzon et al, Eur Radiol 2011; [4] Sardanelli, Breast Cancer Res Treat 2010; [5] Sardanelli, Breast 2010; [6] Kriege et al, New Engl J Med 2004; [7] Leach et al, Lancet 2005; [8] Kuhl et al, J Clin Oncol 2010; [9] Sardanelli et al, Invest Radiol 2011; [10] Hagen et al, Breast 2007; [11] Sardanelli and Podo, Eur Radiol 2007; [12] Lord et al, Eur J Cancer 2007; [13] Warner et al, Ann intern Med 2008; [14] Granader et al, Acad Radiol 2008; [15] Lee et al, Radiology 2010; [16] Kuhl, Radiology 2007(Aug); [17] American College of Radiology, BI-RADS Atlas, 2003; [18] Turnbull et al, Lancet 2010; [19] http://www.eusobi.org/html/img/pool/MIPA_Outline.pdf