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Position Paper

Magnetic resonance imaging of the breast: Recommendations from the EUSOMA working group

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ABSTRACT

The use of breast magnetic resonance imaging (MRI) is rapidly increasing. EUSOMA organised a workshop in Milan on 20–21st October 2008 to evaluate the evidence currently available on clinical value and indications for breast MRI. Twenty-three experts from the disciplines involved in breast disease management – including epidemiologists, geneticists, oncologists, radiologists, radiation oncologists, and surgeons – discussed the evidence for the use of this technology in plenary and focused sessions. This paper presents the consensus reached by this working group. General recommendations, technical requirements, methodology, and interpretation were firstly considered. For the following ten indications, an overview of the evidence, a list of recommendations, and a number of research issues were defined: staging before treatment planning; screening of high-risk women; evaluation of response to neoadjuvant chemotherapy; patients with breast augmentation or reconstruction; occult primary breast cancer; breast cancer recurrence; nipple discharge; characterisation of equivocal findings at conventional imaging; inflammatory breast cancer; and male breast. The working group strongly suggests that all breast cancer specialists cooperate for an optimal clinical use of this emerging technology and for future research, focusing on patient outcome as primary end-point.

1. Introduction

The use of magnetic resonance imaging (MRI) of the breast is rapidly increasing[1] as this technique becomes more widely available and despite the lack of clear evidence of its effectiveness in many clinical settings. It has been firmly established that breast MRI should be carried out routinely with gadolinium-based contrast agent injection except for evaluating breast implant integrity (when unenhanced MRI has been shown to be effective[2]).

The lack of clear evidence is illustrated by the small number of available meta-analyses on breast MRI (Table 1): only 11 from 1995 to June 2009 (0.8 per year over more than 14 years).[3–13]

The European Society of Breast Cancer Specialists (EUSOMA) organised a workshop in Milan on 20–21st October 2008 to evaluate the evidence currently available on the clinical value and indications for breast MRI. Twenty-three experts from the disciplines involved in breast disease management – including epidemiologists, geneticists, oncologists, radiologists, radiation oncologists, and surgeons – discussed the evidence for the use of this technology in plenary and focused sessions. Prior to the meeting, the group performed a literature review on predefined topics; defined questions to be answered at the meeting were identified. This paper presents the consensus reached by this working group on the recommendations for the use of MRI for each indication including, where applicable, a measure of the level of evidence (LoE) from 1a (highest) to 5 (lowest) and degree of recommendation (DoR) from A to D, respectively, using the methodology defined by the Centre for Evidence-Based Medicine, Oxford, United Kingdom,[14] when applicable. Clinical recommendations not based on scientific evidence were explicitly labelled as experts panel opinions (EPO). Following the meeting, the literature review has been updated to June 2009. The working group intends to further update these recommendations as and when new relevant evidence becomes available.

2. General recommendations

We recommend that breast MRI is performed in specialist breast units or in departments of radiology with experience in conventional breast imaging – X-ray mammography (XRM) and breast ultrasound (US) – and in needle-biopsy procedures (under stereotactic or sonographic guidance), as well as in second-look targeted US for findings detected at MRI and not revealed by conventional imaging prior to MRI. A direct link to all other diagnostic procedures, including pathology, should be available. A centre offering breast MRI should perform at least 150 examinations per year. If such a centre does

Table 1 – Published meta-analyses on breast MRI (Pubmed, accessed 26th June 2009 for 'Breast MRI, meta-analyses, on humans, in English').

Topic	1995	1998	1999	2001	2007	2008	Total
Implants	1	1		1			3
Diagnostic performance			1			1	2
High-risk women					1	3	4
Staging						1	1
General on clinical applications						1	1
Total	1	1	1	1	1	6	11

not offer in-house breast MR-guided procedures, it should have an agreement with another institution which offers these procedures within an acceptable time interval. A centre offering MR-guided breast interventional procedures should perform at least 10 procedures per year. General contraindications to MRI and to gadolinium-based contrast agent administration should be taken into account according to international or national guidelines.

3. Technical requirements, methodology, and interpretation

We recommend the use of MR units with magnets with intensity field $\geqslant$1.0 T and gradients $\geqslant$20 mT/m, equipped with bilateral dedicated coils, preferably multichannel. Regular checks using standardized quality control of MR units are recommended, including magnetic field homogeneity, breast coil performance, etc., according to national regulations.

In order to reduce the risk of false positives, we recommend that premenopausal women undergo the examination ideally on day 6–13 of the menstrual cycle, even when oral contraception is used.[15] In case of hormone replacement therapy, we recommend that MRI be performed at least 4 weeks after discontinuation of treatment.[16] These schedule protocols can be waived in urgent cases.

The minimal MRI protocol for breast cancer detection can be defined as follows:

- bilateral (with the exception of prior mastectomy) morphological study using at least one unenhanced high-contrast sequence such as T2-weighted fast/turbo spin-echo with or without fat saturation, short tau inversion recovery (STIR), or spectral presaturation with inversion recovery (SPIR) sequences, with scan plane chosen by the radiologist;

- bilateral (with the exception of prior mastectomy) 2D or 3D gradient-echo T1-weighted dynamic sequence, with or without fat saturation, thickness $\leqslant$3 mm, spatial in-plane resolution $\leqslant$1.5 mm^2 (preferably $\leqslant$1 mm^2), temporal resolution $\leqslant$120 s), scan plane chosen by the radiologist.

We recommend the use of two-compartment (vascular/interstitial) gadolinium-chelates at the standard dose of 0.1 mmol/kg with an injection rate of 2–3 ml/s, followed by saline flushing (20–30 ml at 2 ml/s), preferably using an automatic injector. Additional techniques, i.e. MR approaches not yet validated on a large scale (such as proton spectroscopy, diffusion-weighted and perfusion imaging), must be considered as additional and not a replacement for the above recommended imaging protocols.

The image postprocessing should include temporal subtraction (contrast-enhanced minus unenhanced images) for dynamic studies without fat saturation. Dynamic analysis with generation of percent enhancement versus time curves should be performed through positioning of region of interests at least for all identified enhancing lesions with a diameter $\geqslant$5 mm and mass-like morphology according to the MR imaging Breast Imaging Reporting and Data System (BI-RADS) classification,[17] documenting a representative curve for the most suspicious enhancement dynamics. Subtraction technique and dynamic measurements may not be useful or needed if partial volume effect or patient motion exists.[18] If such artefacts are suspected, unsubtracted images should be visually evaluated and this technical limitation needs to be included in the report.

We recommend the use of standardised interpretation systems such as the above mentioned BI-RADS lexicon,[17] or equivalent. There is some evidence that software for breast MR computer- aided diagnosis (CAD) may be of benefit but insufficient to recommend the routine use of such systems.

A comprehensive diagnostic statement should be included at the end of the report, including the evaluation of the previous conventional breast imaging modalities, when they are available. A final practical recommendation should be suggested at the end of the report. We suggest also attaching to the report itself a selection of paper- or film-printed images that show the relevant findings as described in the report, even though all the images are supplied through the picture archiving and communication system (inpatients) or a DICOM compatible compact disc (outpatients).

We highlight the need of MR-guided procedures (needle biopsy, presurgical localisation) for findings visible only at MRI judged to be suspicious with potential influence on therapeutic decision, as mentioned above. For these procedures, we recommend the use of dedicated coils and devices, officially approved for the procedure.[19] Tissue sampling for histopathology using core biopsy or preferably vacuum-assisted biopsy is required when MR-guidance is used.[20,21]

4. Staging before treatment planning

4.1. *Background*

The basic background to be taken into account is that breast conserving treatment (BCT), including local excision or quadrantectomy plus radiation therapy, is generally accepted as the preferable alternative to mastectomy for tumours up to 3 cm in size. This preference is based on the results of a number of randomised controlled trials (RCTs) with long-term follow-up without significant difference between mastectomy and BCT in terms of mortality rate, confirmed by a recent meta-analysis[22] including long-term follow-up of six RCTs. However, four of the six trials show that mastectomy significantly reduces the risk of locoregional recurrence when compared with BCT, with a significant benefit for mastectomy (pooled odds ratio, 1.561).[22]

This is the main reason for which the surgical treatment in the context of a BCT has always aimed at completely excising the tumoural tissue and at obtaining clear margins, an event which occurs in a not negligible fraction of patients. Kurniawan et al. recently reported from a population-based screening programme that of 1648 women who had conserving surgery, 14% had involved margins, 17% had close ($\leqslant$1 mm), and 70% clear (>1 mm) margins, and that 17% underwent re-excision, of whom 33% had residual disease identified.[23] The importance of obtaining clear margins for ductal carcinoma *in situ* (DCIS) was also confirmed by a recent meta-analysis.[24]

The potential value of preoperative MRI should be discussed in this context.

4.2. *Diagnostic performance of MRI for staging breast cancer*

Excellent data from both single institution[25–31] and multicentre studies[32] exist, which confirm that MRI is more sensitive in the assessment of tumour size, detection of multifocal and multicentric cancers than conventional imaging. In contrast to initial assumptions, MRI also proved to be able to detect DCIS and extensive intraductal component (EIC).[33–39] All studies showed that DCIS and EIC may partly be visible with XRM only, partly with XRM and MRI, partly with MRI alone.

Improved sensitivity of MRI versus XRM could also be proven in a multicentre study with complete and subtle imaging-pathological correlation of complete mastectomy specimens.[40] Neither imaging modality nor the combination of both can detect all malignant lesions (per-lesion sensitivity: MRI 81%; XRM 66%; MRI and XRM combined 82%). An evaluation of the same dataset regarding only DCIS, showed that sensitivity of XRM and MRI, using complete mastectomy specimen as a reference standard, is only 35% and 38%, respectively, 46% by combining XRM and MRI, due to many false negative small DCIS foci.[41]

Studies that focused on the accuracy of assessing the size of DCIS and EIC have shown that MRI (38–64% correct assessment) appears to be more accurate than XRM (27–43%), but neither method can today be considered completely reliable.[42–44] Over- and underestimates of MRI have been reported ranging 11–28% and 17–28%, respectively.

Relevant results were reported for MRI staging of invasive lobular cancers. In a recent systematic review,[45] MRI had a pooled sensitivity of 93% and a high correlation with pathology ($r = 0.81–0.97$); additional ipsilateral lesions were detected in 32% of patients, contralateral lesions in 7%. Surgical management was changed by MRI in 28% of cases.[45] Conversely, it has to be considered that comparing retrospectively women treated for invasive lobular carcinoma or for invasive ductal carcinoma, no significant difference was found for success rate of BCT or for number of surgical operations to obtain negative margins.[46]

Several single institution studies[26,47–49] and one large multicentre study[50] have shown that MRI can detect otherwise occult contralateral malignancy in about 3–4% of the breast cancer patients. However, in the multicentre study, biopsy recommendations just for contralateral lesions occurred in 13% of patients.[50] False positive rates of XRM and MRI may be comparable, that of their combination is on average higher than for XRM alone. The highest rate of correctly diagnosed additional ipsilateral or contralateral foci has been reported for patients with lobular cancer.[45]

An interesting subgroup analysis concerns women at high-risk for breast cancer. The rate of multifocal and multicentric cancers in these women was reported as high as 45–50%.[51,52] In the Italian study, the percentage of breasts with exact detection of the number of malignant lesions was reported to be 0% for CBE and XRM, 33% for US, and 71% for MRI; the percentage of breasts with multifocal or multicentric disease given at least a generic diagnosis of more than one malignant lesion was 14% for both CBE and XRM, 50% for US, and 86% for MRI.[52]

Another interesting subgroup analysis was performed by Deurloo et al.[53] They studied 165 patients eligible for BCT. Preoperative MRI was more accurate than conventional imaging in the assessment of tumour extent in approximately one of four patients. Patients younger than 58 years old with irregular lesion margins at XRM and discrepancy in tumour extent by more than 10 mm between XRM and US had a 3.2 higher chance of accurate assessment at MRI.[53]

Summarising, MRI is certainly the most sensitive method for breast cancer staging in the same or contralateral breast, especially when the already diagnosed lesion is a lobular cancer. For assessment of size of DCIS and EIC, MRI may have better accuracy than other methods, but it is associated with over- and underestimates. A number of malignant lesions remain undetectable for imaging. Suboptimal MR specificity remains an issue and requires MR-guided procedures. However, the practical consequences of any level of specificity should be evaluated according to the specific setting, i.e. taking into account the pretest disease prevalence, here the prevalence of otherwise occult multifocal, multicentric, or contralateral disease in different subgroup patients.

4.3. *Change of treatment planning due to MRI*

Several prospective single institution studies have reported that the findings on breast MRI can change the type of cancer treatment. A correct change in treatment (different surgical access, wider excision, excision of another lesion in the same or contralateral breast) has been reported in 12–32% of patients while an incorrect change has been recorded in 3–30% of patients having preoperative breast MRI.[26,29,53–60]

To evaluate the impact of MRI in breast cancer staging, Houssami et al. pooled the data from 19 studies.[11] A rate of 16.6% of changed surgical management due to MRI was reported on the basis of 12 of these studies and this was composed of:

- 8.1% conversion from wide local excision to mastectomy due to true positive findings;
- 1.1% conversion from wide local excision to mastectomy due to false positive findings;
- 3.0% conversion from wide local excision to wider/additional excision due to true positive findings;
- 4.4% conversion from wide local excision to wider/additional excision due to false positive findings.

Importantly, using tissue needle sampling of suspicious additional lesions discovered with MRI only (through second look US and US- or MR-guided needle biopsy), overtreatment due to false positives can very probably be decreased. In other word, we can expect to largely decrease the 1.1% rate of mastectomies and the 4.4% rate of wider/additional excisions due to MRI findings which turn out to be benign (false positives). The remaining 11.1% rate of MRI-induced correct changes in therapy has to be compared with the rate of local recurrences after BCT (0.5–1% per year).[61,62]

Moreover, the above mentioned 'correct' changes in treatment planning are defined with respect to pathology and to the surgical goal to obtain clear margins as well as to eliminate any residual tumour tissue in the same or contralateral breast. This goal, however, does not consider that radiation therapy, adjuvant chemo- and anti-oestrogen therapies also contribute to eliminating undetected tumours.[61,62] Thus, a diligent evaluation of risks and benefits of the increasingly refined diagnostics is needed for this indication. In fact, the use of MRI was reported to be associated with an increased higher rate of mastectomy according to retrospective data analyses at the University of Philadelphia[63] and at the Mayo Clinic[64,65] while an average delay of treatment by preoperative MRI (and possibly subsequent MR-guided procedures) of 22.4 days has been reported.[66]

Certain patients subgroups have a higher probability of beneficial effect from preoperative MRI.

Candidates for partial breast irradiation (PBI) were evaluated in three recent retrospective studies. Al-Hallaq et al.[67] studied 110 patients initially considered eligible for PBI. MRI found 10% of them affected with multifocal (3.6%), multicentric (4.5%), or contralateral (1.8%) cancer. Patients with false positive findings were 4.5% and the positive predictive value of MRI was 72%. Godinez et al.[68] studied 79 patients (67 with invasive cancer, 12 with DCIS) in a similar setting. Using MRI, they found ipsilateral additional sites of cancer in 30 patients (38%), in 8 of them (10%) in a different quadrant. Finally, Tendulkar et al.[69] reported that in 260 candidates to PBI with 197 invasive cancers and 63 DCIS, MRI identified additional malignant lesions in 11 patients in the ipsilateral breast (4.2%) and in 4 patients (1.5%) in the contralateral breast. Patients with false positive findings were 12.3%. According to these three studies, 5–10% of patients initially considered to be candidates for PBI will prove to be unsuitable for PBI as a result of MRI findings. Noteworthy is a recent consensus statement from the American Society for Radiation Oncology suggesting the use of PBI 'outside a clinical trial' in some patient subgroups.[70]

Limited evidence exists in favour of using MRI for evaluating patients being considered for skin-sparing mastectomy to decide whether or not the nipple can be preserved.[71] This is an issue that partly overlaps with the use of MRI for evaluating the effect of neoadjuvant chemotherapy and the use of MRI in high-risk women (prophylactic mastectomy). Three small series[72–74] have reported in favour of using preoperative breast MRI in patients with Paget's disease of the nipple, but these have included a total of only 30 patients.

Only three retrospective non-randomised studies are available for evaluating patient outcome after preoperative MRI. In 2004, Fischer et al. published a retrospective single institution cohort study on 121 patients who performed preoperative MRI and 224 who did not.[75] They reported no increase in mastectomy rate in women who underwent preoperative MRI and a significantly reduced rate of ipsilateral recurrence (6.8% in the non-MRI group versus 1.2% in the MRI group) as well as of contralateral cancer rate (4.0% versus 1.7%, respectively) during a 40–41-month follow-up.[75] However, the absence of randomisation in these studies introduced significant bias because of the inclusion of smaller and less aggressive tumours in the group who underwent MRI.

Solin et al.[63] reported their experience on 215 patients who performed preoperative MRI and 541 patients who did not, with comparable stage distribution but with a small but significant difference in patients median age at diagnosis (53 and 56 years, respectively). This cohort study did not demonstrate a statistically significant effect of preoperative MRI on recurrence rate (3% versus 4%, respectively), on contralateral breast cancer (6% in either group), or on cause specific survival (94% versus 95%, respectively). However, the authors excluded patients who underwent mastectomy due to extensive disease shown at MRI and we do not know the reasons for having performed MRI in the MR group (denser breast, higher risk, more extended disease at the original conventional imaging studies?). Moreover, 50% of MRI examinations were performed after surgery (with possible negative impact on MRI diagnostic performance) while the authors report an overall re-excision rate of 58%. Peters et al.[76] argue that, based on these data, we have no useful information from which we can assess the potential effect of preoperative MRI in reducing re-excision rates.

Finally, the recent cohort study by Pengel et al.[77] showed an MRI-induced treatment change in 11% of the women (to mastectomy 8.7%, to wider excision 2.3%) and a re-excision rate of 13.8% in the MRI group versus 19.4% in the non-MRI group (not significant probably for a lack of study power). The difference was significant for the subgroup with invasive ductal cancers (1.6% versus 8.1%, respectively).

All considered, we face here the deep methodological flaws that burden retrospective studies when patient outcome end-points are analysed.

A large randomised multicentre study – the COMICE study[78] – has been recently concluded in United Kingdom and a randomised single centre study focused on non-palpable tumours – the MONET study[79] – should be completed during 2010. The COMICE study enrolled more than 800 women each in the MRI and non-MRI groups. A first evaluation presented as a congress abstract[78] showed the MRI-group to be more likely to undergo mastectomy rather than wide local excision (7.1% versus 1.2%) with no significant difference in the number of reoperation needed for clear margins (18.8% versus 19.3%). MRI had a positive predictive value of 62%, a negative predictive value of 84%, and changed management in 6% of patients. However, 28% of suspected multifocal disease was not pathologically confirmed. MRI also correctly detected additional cancerous lesions in 5% of patients, but this did not determine a significant difference in reoperation rate. MRI also had no impact on life quality. We await the final results of the COMICE study and look forward to the publication of the results of the MONET study.

Potential outcome benefits of preoperative MRI could include a lower number of surgical procedures required to achieve free margins, a lower rate of ipsilateral recurrence and contralateral malignancy diagnosed during follow-up after treatment and possibly even improved survival. Note that according to the very large meta-analysis by Clarke et al. on the effect of radiotherapy 'differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce

15-year overall mortality'.[61] However, so far, no clear evidence exists proving that preoperative MRI is beneficial for the final outcome. Existing data cannot exclude a benefit for subgroups, for which further research is needed.

4.4. *Recommendations*

On this background and considering special available information for particular subgroups, we can consider acceptable indications to preoperative MRI with potential advantages for:

(1) Patients newly diagnosed with an invasive lobular cancer (LoE-2a, DoR-B).
(2) Patients at high-risk for breast cancer (LoE-2b, DoR-B).
(3) Patients under 60 years of age with discrepancy in size >1 cm between XRM and US with expected impact on treatment decision (LoE-2b, DoR-B).
(4) Patients eligible for PBI on the basis of CBE and conventional imaging (LoE-3b, DoR-B).

Other recommendations are:

(5) Irrespective of whether the clinical team routinely uses preoperative MRI or not, women newly diagnosed with breast cancer should always be informed of the potential risks and benefits of preoperative MRI if this is under consideration prior to therapy (EPO).
(6) Results of preoperative MRI should be interpreted taking into account CBE as well as XRM and US (whenever XRM and US are indicated); MRI findings with impact on patient treatment should be verified by percutaneous biopsy whenever possible (EPO).
(7) Lesions visible on MRI alone require MR-guidance for needle biopsy with pathological assessment and, if needed, presurgical localisation, implying the availability of specialised equipment and personnel[15,17,80,81] (LoE-1a, DoR-A).
(8) The total treatment delay due to preoperative MRI and possible workup should be no longer than 1 month (EPO).
(9) Possible changes in therapeutic planning resulting from the findings of preoperative MRI should be decided by a multidisciplinary team composed by oncologists, pathologists, radiation oncologists, radiologists, and surgeons (EPO).

4.5. *Research issues*

A special need of RCTs and/or well-designed observational cohort studies on preoperative MRI is identified for the following subgroups with end-point being patient outcome:

(1) Patients with dense breasts: 1a - dense breasts in young women (<40 years of age); 1b - dense breasts associated with intermediate lifetime risk (15–20%) for other factors.
(2) Progesterone-receptor-negative and oestrogen-receptor-negative index tumour.
(3) Patients with involved or close margins on surgical specimen after conserving surgery.
(4) Patients with multifocal, multicentric or bilateral cancer (invasive and/or DCIS), already demonstrated at conventional imaging and pathologically proven.
(5) Patients with unilateral unifocal pure DCIS at conventional imaging (to exclude synchronous ipsilateral or contralateral invasive cancers).
(6) Patients with Paget's disease.
(7) Patients candidate for total skin-sparing mastectomy (evaluation of nipple–areola complex).
(8) Pregnant patients (also testing novel non-contrast MRI techniques, e.g. diffusion-weighted imaging and MR spectroscopy).
(9) Preoperative use of breast MRI after the diagnosis of lesions with uncertain malignant potential (B3) at needle biopsy.

Moreover, the following two research issues are identified:

(10) Techniques for translation of the information of the 3D MRI data set from the radiological environment to the operating theatre, also considering the difference between the prone patient position of MRI and the supine surgical position.
(11) Investigation of the learning curve for the use of preoperative MRI by the radiological–surgical team.

5. Screening of high-risk women

5.1. *Background*

Several genes with high penetrance mutations predispose women to an increased risk of developing breast cancer. Approximately 3% of all breast cancers occur in women with *BRCA1* and *BRCA2* deleterious mutations. A further small percentage occurs in women with *TP53* mutations (Li-Fraumeni syndrome) or rare moderate-penetrance alleles such as *CHEK2*, *ATM* and *BRIP1*, or low penetrance more common alleles.[82] *BRCA* mutation carriers and their untested first-degree relatives should be considered at high risk of breast cancer, with a lifetime risk over 50–60%.

An experts panel from the American Cancer Society[83] recommended annual MRI screening based on evidence for *BRCA* mutation carriers, first-degree relative of *BRCA* mutation carriers and women with a 20–25% or greater lifetime risk as defined by BRCAPRO or other models that are largely dependent on family history. Moreover, they recommended annual MRI screening based on expert consensus opinion for women affected with Li-Fraumeni, Cowden, and Bannayan–Riley–Ruvalcaba syndromes and first-degree relatives and for those who underwent mantle radiotherapy under 30 years of age.[83] On the other hand, they defined that evidence is insufficient to recommend for or against MRI screening based on evidence of lifetime risk for breast cancer for women with 15–20%, lifetime risk and for women with lobular intraepithelial neoplasia, atypical ductal hyperplasia, heterogeneously or extremely dense breast on XRM, and personal history of

breast cancer, including DCIS.[83] Finally, they recommended against MRI based on experts consensus opinion for women at less than 15% of lifetime risk,[83] as it is for the general female population in the United States. The range of lifetime breast cancer risk is wide across populations: cumulative risk (0–84 years) is as high as 18% in some US Registries and, in Europe, ranges from about 6% in Spain, Poland, Estonia, Lithuania, Latvia and Southern Italy to about 15% in Switzerland and Northern Italy.[84]

While some women at high risk opt for bilateral prophylactic mastectomy giving about 90% risk reduction,[85] a larger proportion prefer to undertake screening in an attempt to detect the disease at an early stage to prevent mortality. The rationale for this choice is the extrapolation of mortality reduction obtained with early diagnosis with screening XRM of general female population over 50 years of age.

5.2. *Overview of the evidence*

The high sensitivity of MRI in detecting breast cancer compared to conventional imaging techniques led to cohort studies in the Netherlands,[86] Canada,[87] United Kingdom,[88] Germany,[51] Italy,[52] United States,[89,90] Norway,[91] and Austria,[92] where annual MRI was compared at least with XRM in high-risk women. Five prospective studies on 3571 women with 9652 rounds found 168 patients with breast cancer; pooling their data, MRI showed 81% sensitivity compared to XRM (40%) and US (43%) while only 19% of invasive cancers had nodal involvement.[93]

However, all the studies were observational and not RCTs. This has meant that in order to estimate the benefit for mortality reduction, surrogate end-points should be used. The low rate of nodal involvement (comparable to population XRM screening studies) suggests the MRI screening may be beneficial. As the survival benefit is not known, as well as the degree – if any – of overdiagnosis, it is suggested that national data are collected on high risk screening to determine the acceptability of the test to women and its diagnostic performance. A combined analysis of the Dutch, Canadian, and United Kingdom studies has indicated that doubling time of *BRCA1* and *BRCA2* tumours is 46 and 52 days, respectively, with the rate increasing with age.[94] This suggests that at least annual MRI screening is required. In the MARIBS trial, two radiologists independently read the MRI examinations, giving an additional 10% cancers being detected.[95] This may be an appropriate way to read screening MRI examinations; however more research is needed in terms of interval cancer analysis and trade-off between increased sensitivity and increased needle biopsy rate with double reading.

At cost-benefit analysis, screening high-risk women with annual MRI from age 30[96] or 35[97] is worthwhile. However, as the incremental benefit of MRI screening after 50 years of age could be reduced due to the increased sensitivity of XRM in postmenopausal women, screening with MRI may be not useful as it is in premenopausal women,[96] at least in *BRCA1* mutation carriers.[97] However, it is not known whether women with dense breasts in this age group would derive a benefit from surveillance with MRI as their mammograms are more difficult to read. Moreover, unpublished final results of the Italian study (including also high-risk women with personal previous breast cancer) showed an age distribution of 52 cancers shifted towards older ages: 40% of the cancers in women under 50 and 60% over 50; 33% in 50–59, 21% in 60–69, and 6% over 69.[98]

One additional concern is the radiation dose in the young women with *BRCA* mutation where the breast tissue is believed to be more sensitive.[99] In fact, XRM should be avoided up to 34 years of age as there is no evidence that the benefits outweigh the radiation risks from XRM.[100,101]

When a first cancer is detected by MRI in a high-risk woman and prophylactic mastectomy was not performed, we suggest that subsequent surveillance should be by MRI in order that there is not a stage shift in recurrent disease or in second breast cancer. In the large Swedish study of 123,757 women, 6550 (5.3%) developed synchronous or metachronous contralateral breast cancer. Those who developed it within 5 years and were younger than 50 were 3.9 times more likely to die from their disease than those with unilateral breast cancer. However, those who developed contralateral disease more than 10 years after the primary had the same prognosis as those with unilateral disease.[102] In *BRCA* mutation carriers, the risk of contralateral disease was reported to be 29.5% at 10 years and 40% overall, although it is lower for *BRCA2* carriers compared to *BRCA1* carriers. This risk is reduced after bilateral oophorectomy or treatment with tamoxifen.[103] The high probability of a second breast cancer for high-risk women poses the rationale for including these women in surveillance programmes with MRI.[51,52,87,104]

In a study of 529 women who were opting for prophylactic mastectomy, 5% were found to have occult malignancy (10 invasive cancers and 23 DCIS)[105]; prophylactic mastectomy with sentinel node biopsy was performed in 393 of 529 patients (74%), 178 of whom underwent MRI. Of these, occult cancer was found in 6 of 178 patients (3%), all of whom had negative sentinel node biopsy; preoperative MRI was concordant with prophylactic mastectomy in 4 of 6 cases with occult carcinoma. A similar study in 173 women found a 10% rate of occult disease again with more DCIS (14/19) compared to invasive disease (5/19)[106]; in 59 patients, MRI detected an invasive ductal cancer but missed two DCIS and an invasive ductal cancer. The first study[105] was in favour of preoperative MRI in order to select patients for prophylactic mastectomy without sentinel node biopsy. The second study[106] was against MRI due to cost-effectiveness analysis based on additional economic costs generated by MRI in the health system of United States (1207US$ per patient).

In high-risk women in whom a suspicious lesion is found on MRI, a second look targeted US can localise the abnormality allowing a core needle biopsy to be undertaken. A familial high-risk cohort of 43 women with 48 suspicious lesions on MRI, had a second look US: the lesion was identified and US-guided biopsy undertaken in 67% of cases; in 11/12 cancers, US correctly identified the lesion.[107]

In women who are unable to tolerate MRI, also bilateral whole breast US can be considered. The rationale is given by the ability of this technique to detect cancer in high-risk women, ranging from 33% to 65%, 43% overall, in three studies.[93] In a larger view, we can take into account that in women younger than 50 years with dense breasts and negative mammogram, US yielded an additional 0.4% cancer rate.[108]

5.3. Recommendations

(1) Women with a family history suspicious for inherited predisposition to breast cancer should have their risk assessed by an appropriately trained professional group (genetic counselling). If found at high risk (20–30% or greater), they should be given written information on their risk and on risks and benefits of XRM and MRI screening and alternative risk reducing interventions; if they accept to be screened with MRI, they should be informed on how often and where their screening will take place together with relevant contacts (EPO). Lifetime risk thresholds for including women in surveillance programmes with annual MRI may be selected on the basis of regional or national considerations due to area-specific cumulative risk in the general population, resources availability or practical feasibility (EPO).
(2) High-risk breast screening including MRI should be conducted only at a nationally/regionally approved and audited service or as part of an ethically approved research study. Periodical audit should be undertaken to ensure that high sensitivity is achieved and recall rate (MR imaging more frequently than annual) is less than 10%, and to monitor detection rate, needle biopsy rate and interval cancers (EPO).
(3) Annual MRI screening should be available starting from the age of 30. Starting annual screening before age 30 may be discussed, such as mutation carrier of *BRCA1* or *BRCA2* (starting from 25 to 29) and *TP53* (starting from 20) (LoE-2b, DoR-B).
(4) Annual MRI screening should be offered to:
   – *BRCA1*, *BRCA2*, and *TP53* mutation carriers;
   – women at 50% risk for *BRCA1*, *BRCA2*, or *TP53* mutation that runs in their family (first-degree relatives of mutation carriers);
   – women from families not tested or inconclusively tested for *BRCA* mutation with a 20–30% lifetime risk or greater (LoE-2, DoR-B) (for different thresholds, see point 1);
   – women who have had previous mantle radiotherapy before age 30 (e.g. for Hodgkin disease), starting 8 years after their treatment[109] (LoE-3, DoR-B).
(5) Women at high risk who have been already diagnosed and treated for breast cancer should be included in screening programmes including MRI (LoE-2b, DoR-B).
(6) Definition of upper age limits for non-enrolling women or discontinuing annual MRI is not possible on the basis of current evidence (EPO).
(7) Women of any age undergoing prophylactic mastectomy should have an MRI examination within 3 months before surgery to screen for occult breast cancer (EPO).
(8) Screening XRM should not be performed in high-risk women below 35 years as there is no evidence that the benefits outweigh the risks at this young age (EPO). In *TP53* mutation carriers of any age annual XRM can be avoided based on discussion on risks and benefits from radiation exposure (EPO).
(9) Annual XRM may be considered for high-risk women from age 35 (LoE-2–3, DoR-B).
(10) If annual MRI is performed, screening whole breast US and CBE are not necessary as there is no evidence of any additional benefit to MRI (LoE-2, DoR-B). They are recommended in women under 35 who do not tolerate or have contraindication to MRI or to gadolinium-based contrast material administration (EPO).
(11) Cases requiring workup after MRI should be initially assessed with conventional imaging – re-evaluation of XRM and targeted US (LoE-2, DoR-B). In case of only MRI-detected suspicious findings, MR-guided biopsy/localisation should be performed (LoE-1, DoR-A).
(12) Risk factors such as previous diagnosis of breast invasive cancer or DCIS, atypical ductal hyperplasia, lobular intraepithelial neoplasia, heterogeneously or dense breasts on XRM, when not associated with other risk factors, do not confer an increased risk that justifies the use of MRI screening (EPO).

5.4. Research issues

(1) Models of breast cancer risk evaluation including personal and family history as well as breast density (calculated using digital XRM or non-contrast MRI).
(2) Outcome benefit (survival, QALYs, ect.) of annual MRI in high-risk women.
(3) Risk profile of cancers detected by MRI only, overdiagnosis.
(4) MRI screening for women at intermediate risk.
(5) Added value of double reading of screening breast MRI examinations.
(6) Estimate of the potential harmful effects of radiation exposure from XRM in women with *BRCA1*, *BRCA2* or other deleterious mutations implying a high risk of breast cancer.
(7) Added value of MRI in screening high-risk women over age 50.

6. Evaluation of response to neoadjuvant chemotherapy

6.1. Background

In large breast tumours, neoadjuvant chemotherapy (NAC) is administered prior to surgical treatment with the aim of reducing the tumour to a size that allows for optimal local surgery, preferably BCT. The selection of patients eligible for NAC has become part of patient management by a multidisciplinary team. NAC is usually indicated in two clinical situations:

– inoperable breast tumours at initial presentation;
– large operable breast tumours (stage IIa, IIb, IIIa) not amenable to primary BCT.

In the first situation, surgery cannot be considered because the tumour is fixed to the underlying muscle or invades largely the skin or axillary nodes. In this situation surgery

cannot be performed with the aim of total excision of tumoural tissue and other non-surgical options should be considered. NAC allows to reduce the tumoural mass permitting a secondary potentially curative surgery in 50–80% of the cases.[110–113] The outcome, however, is dominated by the risk of early metastases, which exceeds that of local recurrence and is a predictive factor for poor survival.[114,115]

The second situation is faced when on the basis of CBE and conventional imaging the tumour appears to be unicentric but too large to be treated with conserving surgery such that mastectomy would normally be the recommended treatment. NAC is used in an attempt to reduce the tumour size and achieve secondary conserving surgery. In a meta-analysis published in 2005,[116] the proportion of cases in which a conservative surgery was adopted after NAC ranged from 28% to 89%. However, the proportion of cases primarily amenable for conservative surgery should be taken into account.[117]

Two large trials had a rate of conservative surgery equal to 504/743 (68%) in the NAC arm versus 450/752 (60%) in the adjuvant arm[118] and 120/323 (37%) versus 79/341 (23%),[119] respectively. The rate of patients already candidates for conserving surgery before NAC was 66% in the first trial and 24% in second one. This relatively poor shift from mastectomy to conserving surgery after NAC (2% and 13%) should be also related to the surgeons' attitude for aggressive treatment of locally advanced breast cancer. In a recent report by Chen et al.[120] on 66 breast cancer patients in whom MRI was used for monitoring the response to treatment, of 43 candidates to mastectomy before NAC, 22 (51%) underwent breast conserving surgery. The authors conclude that 'in patients who had more extensive pretreatment disease, despite an excellent response to NAC, the surgeons still tended to apply an aggressive approach and recommended mastectomy. Given that the confirmation of pathological complete response or minimal residual disease would change surgeons' recommendations for less aggressive, conservation surgery, the maturity of MRI for NAC response prediction may provide reliable staging information to aid in the recommendation of the optimal surgical procedure'.

At any rate, the role of MRI seems promising in helping the multidisciplinary team to choose the most appropriate therapeutic planning, in particular surgical treatment aimed at local and regional disease control, by distinguishing unifocal mass tumours with concentric shrinkage after NAC from initially multifocal or multicentric scattered tumours with patchy remaining disease after NAC. This role of MRI is based on its ability to show the real extent of the tumour after NAC. The main problem of this approach is that up to now no RCT has reported demonstrating that the use of MRI as a tool for monitoring the effect of NAC increases the rate of conservative surgery. On the other hand, also in the neoadjuvant setting, MRI may be helpful for accurate surgical decision similarly to the preoperative MRI in absence of NAC (see Section 4).

Moreover, other two possible roles of MRI can be outlined in this setting: early prediction of pathological response after 1–2 cycles of NAC and prediction of disease-free or overall survival.

6.2. *Overview of the evidence*

There is a largely reported clinical experience with breast MRI in the neoadjuvant setting, beginning from 1996 when Kurtz et al.[121] showed this application in 17 patients. However, they firstly noted that a negative MRI after NAC 'does not exclude a residual tumour'.[121] From June 1996 to June 2009, 59 original articles reported the use of MRI in the neoadjuvant setting for a total 2355 patients. However, no meta-analysis is currently available.

Forty studies (enrolling a total 1513 patients) dealt with the prediction of pathological response using validated imaging technique and/or kinetic analysis. Almost all these studies (36 studies enrolling a total of 1385 patients) conclude in favour of the capability of MRI in evaluating the response to NAC. A number of studies showed the MRI ability to assess the response to NAC to be better than that of CBE,[122–127] XRM,[122–124,126–129] or US.[123,127–130] The correlation between residual tumour size at MRI and pathology ranged from $r = 0.65$ to $r = 0.98$.[125,128–135] Four studies[136–139] (128 patients overall) reported a lower performance of MRI.

Underestimation[28,121,125–128,131,135,140–142] and/or overestimation[125,127,128,135,141] of residual disease and false negatives after NAC were highlighted also in other studies even if they reported an overall good evaluation of the potential of MRI for monitoring response to NAC. In the study by Vénat-Bouvet et al.[141] on 41 patients, correct estimate of residual disease was obtained in 71% of patients, underestimate in 23%, and overestimate in 6%. The rates of incorrect estimate were reversed in the study by Kim et al.[135] in 50 patients; they reported 72%, 2%, and 26%, respectively.

Attention was paid to different patterns of tumour reduction after NAC. Patients with mass lesions showing concentric shrinkage seem to be good candidates for conserving surgery while in multifocal/multicentric cancer or solitary masses that show dendritic shrinkage or fragmentation into multiple foci mastectomy should be recommended,[143,144] even though oncoplastic surgery could be used to achieve breast conservation surgery in some of these cases.[145] The probability of underestimating residual disease is reported as being higher for non-mass forming lesions than for mass-lesions.[142] Some authors suggested that the type of chemotherapy agent should be taken into account when using MRI for evaluating the tumour response. Residual disease was frequently underestimated in patients treated with taxane-containing regimens[136] and in HER-2 negative patients treated with bevacizumab.[146]

The ability of MRI to assess the efficacy of treatment early, after 1–2 cycles of NAC, has been reported by studies based on imaging data of volumetric changes,[147–151] kinetic analysis,[152,153] and both.[154]

A retrospective analysis on 254 patients, the largest published study on breast MRI in the NAC setting,[155] reported the results obtained from 2000 to 2007 in one centre where the response to NAC was evaluated mainly using MRI, whereby the NAC regimen was switched if the reduction in largest diameter was less than 25%. This switch happened in 43/254 patients (17%), with 31 (73%) of them showing a favourable clinical response. An increase in conserving surgery was seen in 32% of patients with ductal invasive cancers and in 17% of those with lobular invasive cancers, with

secondary mastectomy because of incomplete resection in 3% and 50%, respectively. A recent study showed that prognostic imaging in this setting is cost-effective, 'assuming that it can be shown the early shift from ineffective neoadjuvant chemotherapy to a more effective one has a measurable benefit in cure rate'.[156]

Breast MRI has also been shown to predict patient outcomes such as the disease-free survival,[149,157] overall survival,[158] and both.[159] Moreover, initial but promising results of non-contrast MR techniques for evaluating the response to NAC have been shown with either proton MR spectroscopy looking at the resonance at 3.2 ppm (total choline containing compounds peak)[160–162] or diffusion-weighted imaging measuring the lesion apparent diffusion coefficient.[163,164]

Summarising, MRI in the NAC setting has been shown clearly to provide better monitoring of NAC effect than CBE, XRM, and US, even though over- and under-estimation of residual tumour occurs, especially for non-mass lesions and tumours fragmented into multiple foci after NAC. The ability of MRI to predict tumour response to NAC has been clearly shown. However, the use of MRI for switching NAC regimen has been shown only in one retrospective study.[155] Several studies have shown the ability MRI to predict patient outcome but the ultimate benefit on survival in patients monitored with breast MRI in the NAC setting is yet to be established.

6.3. Recommendations

(1) MRI does not have a role in the assessment of treatment options in patients with inoperable breast cancer at presentation (EPO).
(2) Pretreatment breast MRI should be performed in patients with large potentially operable breast cancer before the first course of NAC, at the condition that performing MRI does not significantly postpone NAC initiation (LoE-1; DoR-A).
(3) Post-NAC breast MRI should preferably be performed 2 weeks after the last NAC cycle and within 2 weeks before surgery (EPO); treatment delay due to preoperative MRI should not be larger than 1 month (as already stated at point 8 of Section 4.4, point 8).
(4) Variations between pre- and post-NAC should be based on concomitant evaluation of both pre- and post-NAC MRI examinations; even very low enhancement located at the primary tumour site should be considered as a sign for residual disease (LoE-1, DoR-A).
(5) Measurement of residual disease after NAC should be performed according to RECIST or WHO criteria; multifocal or multicentric disease should be evaluated by summing the largest diameter of the visible tumours[165] (EPO).
(6) Caution in interpreting MRI is recommended when patients are treated with taxane or bevacizumab containing regimens (EPO).
(7) Presurgical issues such as verification of multifocal or multicentric disease etc. should be handled as explained in the paragraph on preoperative MRI; the ultimate surgical decision should be based on the relative volume of residual tumour compared to that of the affected breast and decided by a multidisciplinary team (EPO).
(8) In poor responders to NAC, MRI generally confirms the results of clinical and conventional imaging evaluations and may, therefore, not be mandatory (EPO).

6.4. Research issues

(1) Value of non-conventional MR techniques such as contrast-enhanced perfusion studies for kinetic evaluation, diffusion-weighted imaging, and proton MR spectroscopy (single-voxel or 2D/3D chemical shift imaging).
(2) Value of CAD systems for automated tumour volume determination.
(3) Usefulness of additional MR examinations during the NAC aimed at evaluating early and intermediate tumour response.
(4) Clinical value of NAC switching on the basis of MRI data (welcome RCTs).

7. Patients with breast augmentation or reconstruction

7.1. Background

Breast augmentation is increasingly performed for either cosmetic only purposes or to assist cosmesis in the surgical treatment of breast cancer. The number of women with breast implants in the United States was estimated to be between one and two million in 1995.[166] According to the American Society of Plastic Surgeons, 237,000 breast augmentations procedures were performed in that country in 2002 and 347,000 in 2007.[167] In Europe, the overall number of women with implants is unknown.[168]

The vast majority of breast implants used for augmentation contains liquid silicone alone (single-lumen implants) or combined with saline (double-lumen implants). Multiplanar dedicated non-contrast MRI T1- and T2-weighted techniques are used for evaluating implant integrity,[169–172] including fat-suppression with STIR sequences or spectral fat saturation, water/silicone suppression or water/silicone selective excitation. However, radiologists should be aware that at least 14 types of implants have been classified.[173] Thus, women should be exactly informed on the type of implanted prostheses by plastic surgeons and written information should be available for the radiologist when MRI is performed.

The problem of assessing breast implants integrity with MRI has been highlighted by the Food and Drugs Administration in 2006 when this institution re-approved the general use of silicone breast implants with a recommendation for follow-up with an MRI scan biannually, starting in the third year after implantation, in order to detect subclinical implant leakages.[174] This recommendation was based on the report[175] of a rate of breast implant rupture ranging from 0.3% to 77%, with extracapsular gel (i.e. outside the fibrous capsule) in about 12–26% of ruptures. The Institute of Medicine estimated that

in 2000 less than 10% of modern silicone gel-filled breast implants would have ruptured by 5 years and that the rupture rate would continue to increase over time.[175]

Reconstruction is performed with a range of different approaches. Other alternatives than breast implants are more rarely encountered in clinical practice, such as the use of myocutaneous flaps for breast reconstruction.[176,177] Direct polyacrylamide gel injection is also used for breast augmentation, especially in South-East Asia.[178]

7.2. *Overview of the evidence*

Two different settings for the use of MRI in women with breast implants have to be distinguished: (i) implant integrity evaluation, and (ii) breast cancer detection. The latter should be considered also for women with non-implant breast augmentation or reconstruction.

MRI is more accurate than CBE and conventional imaging for assessing implant integrity: while XRM is expected to detect around 25–30% of implant ruptures, MRI will detect the rupture in the region of 78–89%.[6,171,179] In particular, Herborn et al. reported 87% sensitivity and 89% specificity,[179] Hölmich et al. 89% and 97%, respectively.[171] MRI is also the most accurate technique for differentiating intracapsular from extracapsular rupture and for assessing the extent of silicone leakage into the breast and granuloma formation.[180]

In 1998 Chung et al.[181] applied the decision-analysis methodology on this matter. They calculate a pretest implant rupture prevalence in asymptomatic patients of 7%. Their data show that asymptomatic women with a sonographic screening test negative for implant rupture have a probability of a true rupture of 2%. If US shows rupture, the probability of true rupture increases to 38%. However, if US detects a rupture and this was confirmed by MRI, the likelihood of a true rupture rises to 86%. In symptomatic patients with implants $\leqslant$10 years old, implant rupture prevalence was reported to be 31%. If US is negative, true rupture probability goes up to 16%, if US is positive, to 80%, and to 98% if MRI shows rupture. In symptomatic patients with implants >10 years old, the prevalence of rupture was found to be 64%. If US shows rupture, the probability of true rupture increases to 94%.

In 2001, Cher et al.[6] published a meta-analysis including 1039 women from 18 studies with 2036 implants evaluated with MRI and subsequently removed. Most studies involved mainly symptomatic patients and the overall average sensitivity and specificity were 78% and 91%, respectively. The authors reported substantial heterogeneity across studies and generally poor study quality. They concluded that a high achievable positive predictive value justifies the use of MRI in symptomatic women. However, among asymptomatic women, the positive predictive value resulted were too low to warrant use of MRI as a screening tool.

It should be taken into account that the decision-analysis by Chung et al.[181] and the meta-analysis by Cher et al.[6] were published more than 11 and 8 years ago, respectively. This means that both studies include data obtained with outdated MR units and techniques and their results may well be different using modern equipment.

An unsolved problem is the actual rupture rate of asymptomatic implants. Hölmich et al. reported in 2001,[182] a study on 271 women with 533 breast prostheses implanted before 1996 and randomly selected from four plastic surgery clinics in Denmark. They found 26% of implants in 36% of the women examined with MRI to be ruptured, with an additional 6% of implants possibly ruptured. Of the ruptured implants, 22% were extracapsular, significantly associated with previous closed capsulotomy. In a follow-up study,[183] this group of women had another MRI 2 years later: MRI showed 17% of the implants definitely or possibly ruptured. However, silent rupture rate over time is not known for modern silicone gel-filled breast implants. Thus, recommendations might be different according to the year of implantation and type of implants. No reliable data exists on which to base the assessment of any impact on morbidity to support the use of periodical screening with MRI for breast implant rupture.[184]

Breast cancer detection in patients with implants is a different topic. Implants may impair XRM detection of cancer but appear to facilitate tumour detection on CBE.[185] Breast US and MRI may be useful adjuncts in this setting, when MRI should include non-contrast sequences for assessing implant integrity and a contrast-enhanced dynamic study for evaluating mammary gland tissue. The presence of implants does not reduce the sensitivity of MRI for the changes of recurrent disease.[177,179,180]

There is no evidence of increased risk of breast cancer in women with cosmetic breast implants. In other words, silicone breast implants have never been shown to be carcinogenic. In a population of 1763 women who underwent cosmetic breast implant surgery, Friis et al.[186] reported 163 cancers among women with breast implants compared to 137 expected based on general population rates for a standardised incidence ratio equal to 1.2 during a mean follow-up period of 14.4 years. However, women with breast implants had a reduced risk of breast cancer (standardised incidence ratio 0.7) without delayed diagnosis, and an increased risk of non-melanoma skin cancer (standardised incidence ratio 2.1), possibly related to an increased exposure to sunlight. When excluding non-melanoma skin cancer, overall standardised incidence ratio for cancer was 1.0.

Thus, no evidence exists for recommending periodic contrast-enhanced MRI in women with cosmetic breast implants. Asymptomatic women with breast reconstruction after cancer treatment should be candidate for MRI screening only if they are considered at high risk according to the criteria defined in Section 5.3. An added value of contrast-enhanced MRI for recurrence diagnosis in patients with implants after cancer surgery in comparison with CBE and conventional imaging has been suggested by two studies during the 90s.[187,188]

Notably, some kind of breast tissue expanders (used as a first tool in oncoplastic breast reconstruction) should be considered as a contraindication to MRI due to the magnetic marker of the filling valve (Magna-Site injection site). Possible consequences such as overheating, possible expander displacement, possible reduction of magnetisation of the marker are declared by manufacturers (McGhan Medical/INAMED Aesthetics, Santa Barbara, CA; http://www.mrisafety.com/safety_article.asp?subject=16). A case of a woman with this type of expander who underwent a spine MRI and needed breast surgical reintervention was reported.[189]

7.3. Recommendations

7.3.1. General recommendation

Women should be informed about the types of implant prostheses used and the type of reconstructive surgery performed and written information should be available to radiologists when MRI is performed in order to allow the MRI examination to be adapted (sequences and scan planes) to the type of reconstruction/implant (EPO).

7.3.2. Cosmetic breast augmentation

(1) MRI is not recommended as a screening tool for implant rupture in asymptomatic women with breast implants (LoE-1b, DoR-A).
(2) In patients with symptoms suggestive for implant rupture (pain, asymmetry, change in shape, etc.), after conventional imaging, non-contrast MRI is recommended to confirm or exclude rupture (LoE-1a, DoR-A).
(3) In patients with implants and signs/symptoms of parenchymal disease (e.g. breast lump), when conventional imaging is not diagnostic, non-contrast MRI and dynamic contrast-enhanced MRI is indicated to exclude implant rupture and to evaluate the breast gland parenchyma (LoE-3, DoR-C).
(4) In symptomatic patients that have undergone breast augmentation with direct polyacrylamide gel injection, non-contrast MRI and dynamic contrast-enhanced MRI are indicated (LoE-4, DoR-C).

7.3.3. Breast augmentation for oncoplastic reconstruction

(1) In patients with tissue expanders, the MR-compatibility should be evaluated.
(2) In asymptomatic patients routine surveillance with dynamic contrast-enhanced MRI is not recommended for average risk group. It is recommended for higher risk groups that would qualify for MR screening (see above Section 5.3).
(3) In symptomatic women, when conventional imaging is negative or equivocal, non-contrast MRI and dynamic contrast-enhanced MRI are indicated (LoE-2, DoR-B).

7.4. Research issues

(1) New systematic reviews and meta-analyses or decision-making analyses based on recent studies performed on new implant types with updated MR equipments and techniques.
(2) Prospective longitudinal studies investigating the impact on morbidity of preclinical MRI diagnosis of implant rupture.
(3) Prospective longitudinal MRI studies investigating the rate of rupture of new types of breast implants.

8. Occult primary breast cancer

8.1. Background

Occult primary breast cancer has been classically defined as a condition characterised by a histopathologically confirmed cancer of breast type first presenting as a metastatic disease (mainly as axillary lymphoadenopathy) with negative CBE. It represents a type of 'carcinoma of unknown primary' syndrome and accounts for up to 1% of breast cancers.[190,191] To detect the breast origin in these patients has relevant treatment and prognostic implications.[192,193] However, in these patients, XRM detects the cancer in only about one-third of cases.[190] When XRM and US fail to detect the primary tumour and needle sampling or surgical excision of lymphodenopathy allow to suspect the breast origin of the cancer, this condition creates a dilemma with regard to treatment. Treatments reported in literature in those patients are very different, ranging from mastectomy to quadrantectomy, radiation therapy on the breast and the axilla or watchful waiting. Today the suggested intervention is axillary dissection and breast radiation therapy.[194]

8.2. Overview of evidence

Considering ten studies published on this topic from 1997 to 2008,[190–192,195–201] in these patients MRI enables the detection of an occult primary breast cancer in 35–100% of cases. Pooling these results, MRI detected the occult breast carcinoma in 143 of 234 patients (61%). Advantages attributable to MRI for local staging or high correlation with pathological disease extent of disease were reported.[190,192,196,201]

In particular, Olson et al.[191] reported that 16 of 34 women (47%) who underwent surgical treatment preserved their breast and 4 of 5 women with negative MRI who underwent mastectomy had no tumour in the mastectomy specimen. Thus, they conclude that MRI of the breast can identify occult breast cancer in many patients and may facilitate breast conservation as well as that negative breast MRI predicts low tumour yield at mastectomy. More recently, Buchanan et al.[199] reported on a series of 69 patients: MRI found the cancer in 33 (48%) with 15 false positive cases (22%). Of 25 patients with stage II disease and negative or false positive MRI, 12 underwent mastectomy and cancer was found in 4 (33%, negative predictive value 67%), 13 were treated with radiation therapy and nine of them remained without evidence of disease with a median follow-up of 4.5 years.

8.3. Recommendations

(1) Breast MRI is indicated in presence of localised metastatic disease (typically, axillary lymphadenopathy) and negative CBE and conventional imaging (LoE-1b, DoR-A).
(2) Breast MRI is not indicated when extensive metastatic disease exists and/or prognosis is poor, where knowledge of the site of the primary tumour is unlikely to influence the treatment options or the likely outcome (EPO).

(3) If MRI of the breast is negative, surgical treatment of the breast may be avoided (LoE-2b, DoR-B) and therapy planning should be decided by a multidisciplinary team (EPO).

8.4. Research issues

Systematic reviews and meta-analysis of the published studies.

9. Breast cancer recurrence

9.1. Background and evidence overview

The incidence of relapse following BCT is relatively low. Long-term data[62] show an 8.8% cumulative rate of ipsilateral recurrence 20 years after BCT. However, a recent retrospective study[202] on 476 primary invasive cancers with a median follow-up of 5.4 years, reported only 1.7% for ipsilateral recurrence ($n = 8$; mean diameter 1.6 cm) and 2.3% for contralateral cancer ($n = 11$; mean diameter 1.5 cm), 4% overall; of 19 women with ipsilateral or contralateral relapse, 18 were alive and free of metastases.

It is widespread practice to carry out regular breast surveillance with conventional imaging in patients treated by breast conserving surgery. There is no study showing treatment or prognostic benefit from an earlier detection of relapse using MRI as a screening tool in asymptomatic women already treated for breast cancer.

Most suspected relapses detected through conventional surveillance can be confirmed using conventional image-guided biopsy techniques. In a small number of cases it is difficult to definitively exclude recurrence using conventional approaches. MRI is known to have a high sensitivity for recurrent or residual disease also in an early phase after surgery and/or radiation therapy[203] and is recognised as an accurate technique for differentiating surgical scarring from recurrent tumour. Sensitivity of 90–100% with specificities of 89–92% were reported.[204,205]

Finally, relevant results (100% accuracy) were obtained with MRI for the diagnosis of recurrence at the chest wall after mastectomy in a case series of 27 women with clinical and/or US suspicious findings.[206]

9.2. Recommendations

(1) The previous diagnosis of breast invasive cancer or DCIS do not confer an increased risk that justifies the use of annual MRI screening (see Section 5.3, point 12).
(2) If conventional imaging shows a high likelihood of recurrence and needle biopsy can be performed, MRI should not be used as an alternative to needle biopsy (EPO).
(3) In presence of inconclusive findings on conventional imaging for differential diagnosis between scar and recurrence and when needle biopsy cannot be performed or is judged to be probably inconclusive, MRI is indicated (LoE-1b, DoR-A).
(4) The use of MRI for a breast cancer recurrence confirmed with needle biopsy should be regarded as a preoperative MRI (see Section 4).

9.3. Research issues

(1) Systematic reviews and meta-analysis of the published studies.
(2) MRI for diagnosis of recurrence at the chest wall after mastectomy.

10. Nipple discharge

10.1. Background and evidence overview

Nipple discharge is a common symptom. If multiduct or bilateral, breast imaging is not required. However, single duct nipple discharge, is considered an indication for further investigation including XRM and/or US. If the discharge is blood containing, fluid cytology is performed. In the case of single duct nipple discharge, incidence of malignant or high-risk pathology is reported as high as 15%, that of malignancy in case of negative CBE and conventional imaging as high as 10%.[74] Conventional (i.e. XRM) ductography (also named galactography) can be performed but its clinical utility is controversial. Moreover, it is invasive and failure to cannulate or extravasation may occur. Incomplete ductography rate was reported as high al 15% on a series of 163 examinations.[74]

Ten papers have been published on the use of MRI in this setting. Different MRI approaches, including 3D heavily T2-weighted fat-suppressed sequences (indirect MR ductography), dynamic contrast-enhanced study, or – rarely – direct MR ductography (when a diluted gadolinium-based contrast agent was administered through discharging duct cannulation) were used in more than 270 women with suspicious nipple discharge.

Two papers presented a direct comparison between ductography and contrast-enhanced MRI. Krämer et al.[207] studied 35 patients, 16 of them with papillomas demonstrated at pathology. Ductography showed 94% sensitivity (one false negative) and 79% specificity (five false positive) for intraductal papilloma. Of nine cancer cases, XRM combined with ductography demonstrated only one, MRI eight (89% sensitivity); a DCIS was not detected with MRI. Nakahara et al.[208] compared ductography, US, and MRI in 55 patients with bloody nipple discharge and reported that MRI demonstrated all malignant lesions including DCIS. Four cases of DCIS were not visualised by US and three cancers were missed by galactography. Most authors conclude that MRI should not replace ductography in this setting. However, an added value of MRI was reported for improved patient selection and treatment planning, including cancer detection.

10.2. Recommendations

(1) There is insufficient evidence of benefit to recommend the routine use of MRI in the clinical context of suspicious nipple discharge (EPO).

(2) In countries where ductography is considered the routine test for suspicious nipple discharge, non-contrast T2-weighted and contrast-enhanced MRI can be considered if ductography fails for technical reasons or the patient refuses the procedure (LoE-3b, DoR-C).

10.3. *Research issues*

(1) Systematic review and meta-analysis of the published studies.
(2) Value of the different MRI techniques for direct and indirect MR ductography.
(3) Role of MRI in patients with suspicious nipple discharge and negative conventional ductography.

11. Characterisation of equivocal findings at conventional imaging

There is no evidence in favour of breast MRI as a diagnostic tool to characterise equivocal findings at conventional imaging when needle-biopsy procedures can be performed.[12,15,209] This has been also confirmed by a systematic review from the Blue Cross and Blue Shield Association Technology Evaluation Center[210]: the sensitivity of MRI ranged from 91% to 99%. Also considering the 90% sensitivity reported in the meta-analysis by Peters et al.,[13] the use of MRI as an alternative to needle biopsy is associated with an unacceptable risk of missing about 1 of 10 cancers (1 of 20 cancers, considering a 95% sensitivity).

Only in particular cases – such as impossibility to define the site for needle biopsy or if needle biopsy cannot be performed in particular locations – a breast MRI should be performed.[211]

11.1. *Recommendations*

(1) MRI should not be used as an alternative to needle biopsy when needle biopsy can be performed (LoE-1a, DoR-A).
(2) MRI should be considered for cases with abnormal imaging but inconclusive findings on conventional imaging where it is not possible to perform or define a site for needle biopsy (EPO).

11.2. *Research issues*

None.

12. Inflammatory breast cancer

Inflammatory breast cancer accounts for 1–4% of all breast malignancies.[212] The diagnostic challenge is the differentiation from acute mastitis. Excluding papers on the MRI evaluation of the response of inflammatory breast cancers to chemotherapy, from 1994 to 2008, seven papers were published on the use of MRI in this setting, for a total of 139 patients (range 5–48).[212–219] Most authors report a large overlapping of MRI morphologic and kinetic features of the two diseases. MRI may be used in follow-up of presumed acute mastitis in problem cases.[214,216] If after biopsy the diagnosis remains unclear, MRI may help to demonstrate the success of antibiotic treatment and diagnose coexisting/confounding inflammatory carcinoma.[214]

Interesting results were recently reported for the detection of malignant lesions within inflammatory status. Yang et al.[218] compared XRM, US, positron emission tomography combined with computed tomography, and MRI. The last technique was the most accurate in detecting a primary breast lesion.

Moreover, Renz et al. compared 48 inflammatory breast cancers with 42 cases of acute mastitis.[219] No statistical differences were revealed for morphology of masses and of non-mass-like enhancement, breast enlargement, diffuse skin thickening, abnormal nipple configuration, prominent vessels, and also for cutaneous/subcutaneous, perimamillar and diffuse oedema. However, initial and postinitial dynamic characteristics significantly differed between the two groups and in inflammatory cancers more masses with a greater average size were detected. The following morphological criteria were also observed more often in inflammatory cancers: T2-hypointensity of masses (78% versus18%), blooming sign (63% versus 32%), infiltration of pectoralis major muscle (interruption of fat plane, 54% versus 17%; pathological enhancement: 33% versus 7%), perifocal (67% versus 33%), prepectoral (73% versus 31%) and intramuscular pectoral oedema (42% versus 7%). The main localisation of acute mastitis was subareolar, that of inflammatory cancers of inflammatory breast cancers central or dorsal.

The same group of authors[212] compared 48 inflammatory breast cancers with 52 cases of locally advanced breast cancers. The following parameters occurred more frequently in the inflammatory cancers: oedema (cutaneous/subcutaneous 81%, perimamillar 71%, diffuse 90%, prepectoral 73%, intramuscular pectoral 42%); thickening (75%) and pathologic enhancement (60%) of Cooper's ligaments; skin thickening (83%); initially strong, focal enhancement of some dermal or subcutaneous parts followed by slow-continuous enhancement of the surrounding skin (56%).

12.1. *Recommendations*

(1) MRI should not be used for differential diagnosis of inflammatory breast cancers from acute mastitis before treatment (LoE-1b, DoR-A).
(2) If after treatment of a presumed mastitis doubts remain about the presence of an underlying breast cancer, MRI can be considered (LoE-2b, DoR-C).

12.2. *Research issues*

Prospective studies on the value of MRI for differential diagnosis of inflammatory breast cancers from acute mastitis before/after treatment.

13. Male breast

Male breast cancers account for approximately 1% of all breast cancers. The American Cancer Society estimates that about 2000 new cases of invasive breast cancer are diagnosed in men each year and approximately 450 men die from breast cancer annually in the United States.[220] Only one paper is available on the use of contrast-enhanced MRI for studying breasts in males,[221] demonstrating that benign and malignant breast diseases have the same imaging features in men and women. No evidence exists in favour of an added value of MRI for the diagnosis of breast cancer in men.[222] Schininà et al.[223] showed a better performance of an MRI-unenhanced fat- suppressed T2-weighted scan compared to US in order to distinguish gynaecomastia from pseudogynaecomastia (also said lipomastia) in 19 adult males HIV patients treated with high-activity antiretroviral therapy.

13.1. *Recommendation*

MRI should not be used for routine diagnosis of breast cancer in men (EPO).

13.2. *Research issues*

Prospective studies comparing unenhanced MRI, XRM, and US in differential diagnosis of gynaecomastia from pseudogynaecomastia, follow-up and treatment planning of both diseases.

14. Conclusions

Breast MRI is an imaging technique that is increasingly being used in clinical practice. However, it should not be used when it is not indicated. This document highlights the indications for which evidence can be found in the literature or a consensus opinion has been reached. However, there remain many research issues deserving of high quality primary studies and secondary studies (systematic reviews, meta-analyses, and decision-making analyses) in order to clearly define clinical efficacy/effectiveness and indications of this diagnostic technology. Technical improvements, such as very high spatial resolution and innovations such as diffusion-weighted imaging and proton spectroscopy, are expected to enter clinical practice in the near future. Breast cancer specialists should work together to ensure the optimal clinical use of this emerging technology and for future research focusing on patient outcome as the primary end-point.

Conflict of interest statement

None declared.

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