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INVITED COMMENTARY

Additional findings at preoperative MRI: a simple golden rule for a complex problem?

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Preoperative magnetic resonance imaging (MRI) is a hot topic, a complex problem which probably will remain unresolved for several years.

The starting point is the great body of evidence for the higher sensitivity of MRI compared with mammography and ultrasonography (US) in detecting malignant lesions in the breast harboring the index cancer [1] and in the contralateral breast [2]. However, the discussion about advantages [3] and disadvantages [4] is challenging [5].

Potential advantages of preoperative MRI can be summarized as follows:

1. better short-term patient outcome (reduced re-excision rate; reduced amount of removed tissue due to a tailored surgical strategy);
2. better mid-term patient outcome (reduced rate of ipsilateral local recurrence and contralateral cancer);
3. better long-term patient outcome (longer disease-free and overall survival); and
4. better psychological patient status due to the use of the most sensitive tool for local staging.

However, none of these potential advantages have been clearly demonstrated by high-level studies, i.e., by a large multi-institutional randomized controlled trial (RCT). On the other side, drawbacks of preoperative MRI can be outlined as follows:

1. overtreatment due to false positive MRI findings;
2. overdiagnosis and overtreatment of malignant additional lesions which could have been cured by radiotherapy and/or systemic adjuvant chemotherapy or hormone therapy;
3. delay in definition of surgical strategy due to difficult managing of MRI additional findings, especially those visible only at MRI, hence requiring an MR-guided needle biopsy and/or localization; and
4. increase in patient anxiety due to treatment delay and/or uncertainties related to the interpretation and management of additional findings.

Obviously, advantages and disadvantages can be mixed in variable combinations. The problem is hard because we have in our hands a technique surely being the best option for evaluating ipsilateral disease extent and possible contralateral cancers but we are not sure that, using this technique, we have a better treatment for our patients. We could have a worse (i.e., an avoidable more aggressive) treatment. Moreover, patients know that MRI is highly sensitive and self-referred presentation is possible.

Looking at the secondary evidence, meta-analyses found a rate of more aggressive surgery for true positive MRI findings of 11.1% for the ipsilateral breast [1] and 4.1% for the contralateral breast [2]. The rate of MRI-induced ipsilateral wider surgical treatment should be compared with the rate of positive margins after breast conserving treatment (BCT), reported to be from 20 to 40% or more, and that of local recurrences after BCT, usually considered from 5 to 10% at 10 years and reported about 9% at 20 years. The rate of MRI-induced contralateral surgery for synchronous cancer should be compared with 0.5–1%

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annual risk of contralateral breast cancer in women with a previous history of breast cancer [3]. Notably, only ipsilateral recurrences or contralateral cancers which would have appeared in the first years after a conservative treatment might be avoided by preoperative MRI. Thus, we obtain a relatively balanced result for the contralateral breast: 3–4% of MRI-detected contralateral cancers versus 2–3% cumulative rate of expected contralateral cancers. Conversely, we have an 11% of MRI-induced wider ipsilateral surgery versus and only 2–3% of cumulative rate of expected ipsilateral recurrences [3].

As a consequence, the risk of overdiagnosis and overtreatment by preoperative MRI is probable at least for the ipsilateral breast. However, we must consider that: (a) the rate of MRI-detected ipsilateral and contralateral cancers is probably overestimated due to the fact that preoperative MRI has been performed in non-consecutive (selected) patients with a probable higher likelihood of these lesions; (b) a publication bias can be hypothesized; (c) ipsilateral and/or contralateral overtreatment could be compensated by the reduction of additional surgical interventions needed to achieve free margins; and (d) considering the role of radiation and systemic therapy, a patient-based perspective should evaluate the combined effect on both breasts. This last point means that MRI could determine an unnecessary ipsilateral excision but also anticipate the diagnosis of a contralateral cancer—or vice versa—avoiding the future second cancer event. For an individual patient, preoperative MRI may determine a spectrum of possibilities from a bilateral advantage to no change of treatment planning to a bilateral overtreatment [3]. Finally, if preoperative MRI would be demonstrated to increase disease-free or overall survival, then overdiagnosis and overtreatment would change in simple diagnosis and treatment. However, this is beyond the current strategic horizon.

A shared consensus was recently reached by an interdisciplinary working group promoted by the European Society of Breast Cancer Specialists (EUSOMA) in considering the following four indications for preoperative MRI [5]:

1. patients newly diagnosed with an invasive lobular cancer;
2. patients at high risk for breast cancer;
3. patients under 60 years of age with discrepancy in size >1 cm between mammography and US with expected impact on treatment decision; and
4. patients eligible for partial breast irradiation on the basis of clinical breast examination and conventional imaging.

My personal view is that other two groups of women could be considered for preoperative MRI [3]:

5. women with mammographically heterogeneously or extremely dense breast and
6. women with a multifocal or multicentric or bilateral cancer already diagnosed at conventional imaging.

The indication concerning invasive lobular cancer is in agreement with the study recently published by Mann et al. in this journal [6]. With the limitation of a retrospective design, they demonstrated a significant reduction in the re-excision rate in the women who did undergo preoperative MRI (9%) versus those who did not (27%) without any increase either of mastectomy rate (48% vs. 59%) or mean time to final pathology (40 vs. 44 days, respectively) [6]. Thus, the paradigm is inverted showing the possibility to use MRI preoperatively with the aim to reduce the aggressiveness of surgical treatment.

However, all nonrandomized studies on this matter have intrinsic bias and limitations. This is true also for other retrospective studies which reported results in favor [7] or partially in favor [8] of preoperative MRI as well as for retrospective studies which reported results against [9–11] preoperative MRI. Two interesting small studies from a Japanese group showed important advantages of a surgical approach precisely tailored on the basis of preoperative MRI performed in supine surgical position. In one non-randomized study [12], they demonstrated significantly reduced excision area and additional excision rate compared to US-guided dye application in the surgical treatment of invasive ductal carcinomas after neoadjuvant chemotherapy. In a second study [13], they randomized 52 patients with localized ductal carcinoma in situ: 24 of them received breast conserving surgery (BCS) using projection and reproduction techniques of surgical position breast MRI; 28 of them underwent conventional prone-position breast MRI and BCS using mammography-guided hook-wire. Average volume of the pathologic specimens in the new technique group was significantly smaller than that in the conventional BCS group (27.5 cm^3 vs. 57.6 cm^3) while the positive margin rate was significantly lower (12.5% vs. 39.3%, respectively). These experiences indicate that a precise MRI-based tailored BCS is the way for the future, as is shown also by a recent research on US navigation of breast MRI volumes acquired in supine position [14]. The key point is the translation of three-dimensional (3D) information from the MR room to the operating theatre.

Preoperative MRI is a typical matter which should be solved by means of large RCTs. This is due to the fact that this use of breast MRI is not for a simple diagnosis (we are already aware of the index cancer). It may seem a paradox, but preoperative MRI is a kind of screening looking for other cancers than the index one. If the results of preoperative MRI impact on treatment, then this diagnostic tool should be regarded as a therapy.

Few months ago, the results of the COMICE trial came to publication [15]. The investigators enrolled more than 1,800 women with a newly diagnosed breast cancer randomized into two groups, with ($n = 816$) and without ($n = 807$) preoperative MRI. The reoperation rate (primary end-point) was 19% in both groups; the total mastectomy rate was 13% versus 9%, respectively. These results are important. They show the possible consequences of a suboptimal use of preoperative MRI. Several limitations of the study have been already discussed [16]. Importantly, the investigators faced a very slow enrollment by a large number of centers, with many of them enrolling less than 4–5 patients/year, only 2–3 randomized to MRI. The results show no systematic use of needle biopsy and localization (including MR-guided procedures), with many cases of changed treatment due to unverified false positive findings. Regarding the initial surgical treatment in the MRI arm, the investigators say: "Of the 58 patients, who underwent a mastectomy, 32 had an additional biopsy, 11 did not have a biopsy, and data were unavailable for the remaining 15 patients. Of the 16 patients who underwent an avoidable mastectomy, three did and six did not have a biopsy, and data are missing for the remaining seven patients" [15].

In this large RCT, the management of MRI additional findings has been a key point. In this perspective, an expert use of second look targeted US is essential. This requires not only to be familiar with (supine) breast US but also with (prone) breast MRI as well as with the different lesion locations at the two imaging techniques. Six recent studies reported percentages of US correlate for initially MR-detected findings variable from 46 to 82% [17–22]. Pooling their results, we have a total of 1,208 findings, 759 of them with a US correlate (63%). While the mean malignancy rate is 27% (range, 22–29%), that of lesions with a US correlate is 32%, (range, 27–36%), and that of lesion without a US correlate is 18% (range, 10–28%), showing a variability of results probably depending also on the local experience and expertise for targeted US examination. Thus, MR-guided procedures are necessary only in a minority of cases, those where targeted US fails to find the MRI finding. However, the rate of malignancy of MRI findings without US correlate does not go below 10% also when the rate of US detection reaches 82% [17].

In this context, in the current issue of this journal, Elshof et al. [23] report their experience on 690 consecutive patients with 698 pathology-proven index cancers planned for BCT based on clinical examination and conventional imaging who underwent preoperative breast MRI. MRI additional findings were prospectively managed without using MR-guided procedures. They defined additional findings located within a 3-cm 3D space including the index tumor as "multifocal", those located outside that space as "multicentric", and those in the other breast as contralateral. Multifocal findings were not sent to targeted US, and these findings typically led to BCS with larger excision to include the additional findings. Multicentric and contralateral findings were sent to targeted US. If they were found, then needle biopsy was performed. If malignant disease was confirmed over a region too large to allow cosmetically acceptable conserving treatment, then mastectomy was planned. The key rule of this approach is as follows: *If pathology proof could not be obtained (i.e., if targeted US failed to find the lesion), then the therapy plan was not changed and follow-up was advised.*

At preoperative MRI, 141 additional findings were detected in 121/690 patients (18%). MRI additional findings without pathology proof—named unidentified bright objects (UBOs) by the authors—were found in 81/690 patients (12%). Importantly, of 141 additional findings, 44 multicentric and contralateral findings (31%) were followed up at least with conventional imaging (40 of them being MRI BI-RADS 3). The median follow-up was 55 months (range, 22–103 months). In none of the patients these findings turned out to be detected as suspicious and confirmed to be malignant (only four additional findings were lost to follow-up). Multifocal lesions were significantly more often malignant than multicentric and contralateral lesions.

This approach resulted in a rate of change of surgical planning inferior to 10%, composed of mastectomy for 24 breasts in 23/690 patients (3.3%), wider ipsilateral excisions in 40/690 patients (5.8%), and contralateral excision in 3/690 (0.4%). Of 40 wider ipsilateral excisions, 32 (80%) were pathologically confirmed after surgery.

This experience contains a golden rule and a possible misleading message, the latter already acknowledged by the authors. The *golden rule* is: Do not convert a BCS to mastectomy on the basis of MRI additional finding(s) not pathologically verified to be malignant. The possible *misleading message* is: The use of MR-guidance is not necessary in the preoperative setting.

To perform mastectomy or contralateral surgery for MRI additional findings without needle biopsy verification of malignancy should be regarded as malpractice. Moreover, MR-guided biopsy should be integrated in clinical practice as it was for needle biopsy under stereotactic guidance. A large experience in MR-guided biopsy is reported in the literature, including a large prospective multi-institutional study of 538 lesions [24], many recent single-center experiences [25–31], also evaluating problems and limitations [32–35], as well as the results of a multidisciplinary consensus meeting on the use of vacuum-assisted MR-guided biopsy [36]. The mean time needed for an MR-guided procedure is not different than that of a stereotactic biopsy in the film-screen era: about 45 min

[37]. Using MR-guidance, the rate of unnecessary ipsilateral wider excisions reported by Elshof et al. [23]—8/40 (20%)—could have been drastically reduced. Also MR-guidance has limitations and some findings can be difficult or impossible to be reached. In these cases, the *golden rule* by Elshof et al. should be applied. Notably, the application of this rule demonstrated that multicentric and contralateral findings without US correlate were not detected as malignant at follow-up. However, we do not know how many of them were benign and how many of them were malignant but cured by radiation or systemic therapy.

The general recommendations of the EUSOMA interdisciplinary working group still appear to be valid:

1. 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 before therapy;
2. results of preoperative MRI should be interpreted taking into account clinical breast examination as well as mammography and US (whenever mammography and US are indicated);
3. MRI findings with impact on patient treatment should be verified by percutaneous biopsy whenever possible;
4. lesions visible on MRI alone require MR-guidance for needle biopsy with pathological assessment and, if needed, presurgical localization, implying the availability of specialized equipment and personnel;
5. the total treatment delay due to preoperative MRI and possible workup should be no longer than 1 month; and
6. possible changes in therapeutic planning resulting from the findings of preoperative MRI should be decided by a multidisciplinary team [5].

At any rate, the use of preoperative MRI remains an open issue and high-quality research using the patient's outcome as primary end-point is still warranted.

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