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Original article

Overview of the role of pre-operative breast MRI in the absence of evidence on patient outcomes

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A B S T R A C T

The role of pre-operative breast MRI is outlined on the basis of the existing evidence in favor of a superior capability in comparison with mammography and sonography to detect ipsilateral and contralateral malignant lesions and to evaluate the disease extent, including the extensive intraductal component associated with invasive cancers. Patients with a potential higher anticipated benefit from pre-operative MRI can be identified as those: with mammographically dense breasts; with a unilateral multifocal/multicentric cancer or a synchronous bilateral cancer already diagnosed at mammography and sonography; with a lobular invasive cancer; at high-risk for breast cancer; with a cancer which shows a discrepancy in size of >1 cm between mammography and sonography; or under consideration for partial breast irradiation. More limited evidence exists in favor of MRI for evaluating candidates for total skin sparing mastectomy or for patients with Paget's disease. 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 pre-operative MRI; results of pre-operative MRI should be interpreted taking into account clinical breast examination, mammography, sonography and verified by percutaneous biopsy; MRI-only detected lesions require MR-guidance for needle biopsy and pre-surgical localization, and these should be available or potentially accessible if pre-operative MRI is to be implemented; total therapy delay due to pre-operative MRI (including MRI-induced work-up) should not exceed one month; changes in therapy planning resulting from pre-operative MRI should be decided by a multidisciplinary team.

Background

Breast conserving treatment (BCT), comprising breast conserving surgery (BCS) plus radiation therapy, is equally effective to mastectomy, in terms of survival, for early-stage cancers as demonstrated in randomized controlled trials (RCTs) and confirmed in a meta-analysis.[1] BCT is generally considered the preferred treatment option in early-stage disease, although treatment decisions are ultimately dependant on the woman's preference. Of importance, four of the six RCTs of BCS included in meta-analysis show a significantly lower risk of locoregional recurrence in favor of mastectomy (odds ratio 1.561).[1] From this viewpoint, BCS should always aim to completely remove tumoral tissue and obtain clear margins.

Evidence on MRI's detection capability

Evidence exists that MRI has a superior sensitivity compared with mammography in assessing index tumor size and in detecting ipsilateral multifocal or multicenter cancers as demonstrated also in a multicenter study.[2] MRI may fail to detect all cancers when the whole breast is used as a pathological reference standard,[3] especially when ductal carcinoma in situ (DCIS) is considered.[4] The advantage of MRI relative to mammography has been shown to be non-significant in fatty breasts, while significant in scattered fibroglandular and heterogeneously or extremely dense breasts.[3] MRI has also been shown to detect extensive intraductal component, but may overestimate this finding in 11–28% of cases and underestimate it in 17–28%.[5–7] In a meta-analysis of 19 studies[8] for the breast harboring a proven index cancer, with a median MRI-detection of 16.6%, the impact of pre-operative MRI on surgical planning was evaluated for 12 studies reporting surgical outcomes as follows[8]:

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- 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.

Furthermore, several studies have shown that MRI can detect otherwise occult contralateral malignancy in women newly diagnosed with invasive cancer, as shown also in a large multicenter setting for about 3% of patients, with a trade-off in terms of additional needle biopsy for benign findings.[9] A very recent meta-analysis of 22 studies[10] showed that MRI yields an incremental cancer detection rate over conventional imaging equal to 4.1% with a positive predictive value of 47.9% due to a false positive detection rate of 5.2% (true positives/false positives ratio = 0.92). In this analysis[10] (and where studies reported on tumor stage) 35% of contralateral cancers were DCIS with a mean diameter of 7 mm, 65% invasive with a mean diameter of 9.3 mm, the majority of the latter were node negative[10].

A higher probability of an added diagnostic value of MRI for local staging has been shown for particular patient subgroups. In a recent systematic review of patients with invasive lobular cancer, additional ipsilateral lesions were found to be detected with MRI in 32% of cases, contralateral lesions in 7% while surgical management was changed in 28%.[11] In these patients, MRI showed a 93% pooled sensitivity and a high correlation with pathologic tumor extent.[11] Women with an inherited high risk for breast cancer have a high probability of a more accurate local staging with MRI. The rate of multifocal and multicenter cancers in these women was reported as high as 45–50%.[12,13] In one study, the percentage of breasts with exact detection of the number of malignant lesions was reported to be 0% for mammography, 33% for sonography, and 71% for MRI.[13] If a cancer is diagnosed in a high-risk woman, MRI probably adds staging information.

Regarding the assessment of tumor extent, a retrospective analysis by Deurloo et al[14] reported that patients younger than 58 years of age with irregular lesion margins at mammography and discrepancy in tumor extent (including spiculated lesions and suspicious microcalcifications) by more than 10 mm between mammography and sonography, had a 50% probability of complementary value of MRI over conventional imaging versus 16% in the remaining patients (3.2-fold higher probability, positive predictive value 50%, negative predictive value 84%).

Last but not least, MRI identifies a fraction of candidates for partial breast irradiation (PBI) who are affected with multifocal, multicentric, or contralateral cancer and may therefore not be suitable for this approach in treatment. According to three recent studies, this occurs in about 5–10% of women who were initially thought to be suitable for PBI, but were ineligible based on pre-treatment MRI.[15–17] The American Society for Radiation Oncology has recently established the possibility of using PBI "outside a clinical trial" at least for patient subgroups.[18]

Up to now, we have lacked evidence on patient outcomes in favor of, or against, pre-operative MRI. The results of two RCTs – the COMICE[19] and the MONET[20] studies – are awaited, although very early data from COMICE have not indicated benefit from MRI. Conflicting retrospective studies on outcomes have been reported,[21–24] intrinsically limited by the absence of randomization.

The potential and the drawbacks of MRI

Using tissue needle sampling of MRI-detected additional findings (through second-look sonography or MR-guidance), we will potentially drastically reduce overtreatment due to MRI false positives. As a consequence, using the estimates of Houssami et al.,[8] we would have only the 11.1% rate of MRI-induced potentially correct changes of surgical planning for the breast harboring the index lesion. To place this into context, we should consider the routine rate of positive margins after BCS, ranging from 20% to 40% or more,[25] and that of local recurrences after BCT, usually considered from 5% to 10% at ten years[26] and reported about 9% at 20 years.[27]

A similar reasoning can be proposed for the detection of contralateral cancers. Consistent use of MR-guided biopsy could strongly reduce the surgical treatment of false positives (about 5%)[10], offering the chance to treat the synchronous contralateral cancers in about 4% of the women[10] with simultaneous surgery. This rate should be compared with the 0.5–1% annual risk of contralateral breast cancer in women with a previous history of breast cancer.[28,29] We could speculate that only ipsilateral recurrences or contralateral cancers which would have appeared in the first years after BCT might be avoided by pre-operative MRI.[26] Thus, this comparison gives a relatively balanced result for contralateral cancers: with a 0.75% annual rate of contralateral cancers and an anticipated MRI diagnosis up to 3–4 years, we have a 2–3% cumulative rate of contralateral cancers in the first few years to be compared with a rate of MRI-detected contralateral cancers of 3–4%.[9,10] A larger discrepancy is obtained if we hypothesize a similar cumulative rate (2–3%) for local recurrences in the first years, to be compared with the 11.1% rate[8] of MRI-induced correct changes of surgical planning for the breast harboring the index lesion. However, the rate of MRI-detected ipsilateral and contralateral cancers is probably overestimated due to the fact that pre-operative MRI has been performed in non-consecutive (selected) series[26], i.e. through selection of patients with a probable higher likelihood of ipsilateral and contralateral cancers (for example dense breasts, or high-risk patients) to MRI. A publication bias is also hypothesized.

Moreover, it is hard to evaluate the combination of the two aspects from a patient-based perspective: pre-operative MRI could determine an unnecessary wider/additional ipsilateral excision but also anticipate the diagnosis of contralateral cancer (or vice versa), thus avoiding the second cancer event in future, and receiving treatment for both breasts upfront; it may be argued that a bilateral advantage or a bilateral overtreatment could happen as a consequence. This interpretation considers the fact that systemic therapy may prevent some of the contralateral cancers [26] detected upfront by MRI only.

At present, potential outcome benefits of pre-operative MRI may include a possible reduction in the rate of the following events: surgical intervention needed to achieve free margins; ipsilateral recurrences; secondary mastectomies; and contralateral malignancy. On the other hand, we should consider that the use of MRI has been reported to be associated with an increased higher rate of mastectomy[22,26,30,31] and with a treatment delay of 22.4 days.[24]

Perspectives on indications for pre-operative MRI

Acceptable indications for pre-operative MRI can be presently defined for subgroups of patients in whom a larger potential benefit in term of local staging might be expected. This approach should be considered also for future RCTs evaluating pre-operative MRI. In fact, if the advantages of MRI would be relevant only for particular subgroups, RCTs on the average population of women newly diagnosed with a breast cancer may dilute the benefit and probably reduce power for achieving significance in subgroup analysis. Patients with a potential higher anticipated benefit from pre-operative MRI can be identified as those:

1. with mammographically (heterogeneously or extremely) dense breasts;
2. with a unilateral multifocal/multicentric cancer or a synchronous bilateral cancer;
3. with a lobular invasive cancer;
4. at high-risk for breast cancer;
5. with a cancer which shows a discrepancy in size of >1 cm between mammography and sonography; or
6. under consideration for PBI.

More limited evidence exists in favor of MRI for evaluating candidates for total skin sparing mastectomy in order to decide saving or not the nipple[32] or for patients with Paget's disease.[33–35] Further research is needed in particular on these indications.

Irrespective of whether the clinical team routinely uses pre-operative MRI or not, the following issues are paramount:

A. women newly diagnosed with breast cancer should always be informed of the potential risks and benefits of pre-operative MRI;
B. results of pre-operative MRI should be interpreted taking into account clinical breast examination, mammography, sonography and verified by percutaneous biopsy;
C. MRI-only detected lesions require MR-guidance for needle biopsy and pre-surgical localization, and these should be available or potentially accessible if pre-operative MRI is to be implemented;
D. total therapy delay due to pre-operative MRI (including MRI-induced work-up) should not exceed one month;
E. changes in therapy planning resulting from pre-operative MRI should be decided by a multidisciplinary team.

5. Conclusion

In reality, and considering the detection capability of MRI, we cannot wait for conclusive evidence in favor of or against pre-operative MRI. To deny this examination to all women newly diagnosed with breast cancer is a questionable decision because the evidence is 'uncertain' rather than against a benefit from pre-operative MRI. In this context, to define general rules to be shared by breast cancer specialists is the first goal to avoid inappropriate use of this diagnostic step. To propose pre-operative MRI for subgroups of women as here defined can be a practical strategy for the present. Finally, the woman's preference should be also carefully considered in order to decide whether to perform or not to perform pre-operative MRI, according to evidence-based medicine basic principles.[36] From this standpoint we should also consider that mastectomy in 2010 is no longer the same surgical approach performed thirty or forty years ago. Immediate reconstruction, skin- and nipple-sparing mastectomy changed the scenario at least in terms of cosmetic results. Part of the reported increase in mastectomy rate may be due to the availability of these options.

The large meta-analysis of Clarke et al. on the effect of radiation therapy concludes that "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".[37] MRI is not radiation therapy but guiding a more effective surgery might potentially provide a similar effect. High-quality clinical research on pre-operative MRI is needed, especially RCTs.

Conflict of interest statement

None declared.

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