Breast Care Day

The day-long symposium devoted solely to recent developments in breast imaging which traditionally takes place on the first day of the ECR annual congress, namely the Siemens Healthineers-sponsored Breast Care Day, is fast becoming a must-attend fixture of the congress. With a cast-list of speakers prominent in their field, this year's Breast Care Day was the most successful ever — more than 1300 radiologists attended the morning, lunch and afternoon sessions.

This article summarizes a selection of some of the papers presented at the Siemens Breast Care Day, which also benefitted from cooperation with Bayer Healthcare.

Preoperative Breast MRI: first results from the MIPA study

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To set the scene Prof. Sardaneli pointed out that opinions regarding pre-operative breast MRI are sharply divided between professionals who are against, those who are for and the rest who are undecided as to its value.

The recommendations of the American Society of Breast Surgeons are however clear: don't routinely order breast MRI in new breast cancer patients. The question then becomes how routine is routine?

It is well accepted that breast MRI provides information about tumor extent but whether this should be used to determine tailored treatment is a complex question since there is always the danger of overdiagnosis and subsequent overtreatment such as an increased number of mastectomies. Several years ago the working committee of the EUSOMA group on the various applications of breast MRI was undecided about breast MRI with finally a difficult consensus being established for its use in several scenarios: for newly diagnosed invasive lobular cancer; cancer in high risk women; discrepancy in lesion size between mammography and ultrasound and for eligibility for partial breast irradiation (PBI). (Of note, in the context of PBI a recent meta-study showed that approx. 11% of women originally considered suitable for PBI were found to be in fact not suitable for PBI after MRI). It shouldn't be forgotten that breast MRI images acquired for one of many valid diagnostic reasons (e.g. in high-risk women or for monitoring neo adjuvant chemotherapy, for occult breast cancer, etc.) already constitute a pre-operative MRI. The real issue is whether an MRI image should be acquired expressly for pre-operative use in women with breast cancer but without any existing MRI images. This is in fact a complex question since the sensitivity/specificity characteristics of MRI do not, according to strict Evidence-Based Medicine criteria, justify its use as a screening tool for example in contralateral breast screening.

However there have been two randomised controlled trials (RCTs) whose results favour the use of pre-operative MRI for reducing reintervention for positive surgical margins. But there are also two RCTs whose results argue against such use. Several observational studies have confirmed the high sensitivity (and also specificity) of breast MRI but the question remains how to assess the clinical impact of pre-operative MRI in terms of outcome for the patient. The problem with such observational studies of women having MRI is that there are no corresponding data for women who have not had MRI.

THE MIPA TRIAL

All this provides the background rationale for the **Multicenter International Prospective Analysis (MIPA)** pre-op breast MRI study. This is an on-going observational

The first results of the MIPA trial. The main message is that pre-planning of a mastectomy based on mammography/ultrasound data prompts an MRI scan (frequently requested specifically by a surgeon who wants the assurance of MRI prior to carrying out the surgery). The MRI scan does not result in the carrying out of more mastectomies

2017 Breast Care Day Video recordings
Videos of all presentations are available at www.siemens.com/breastcareday

non-randomized trial. Up to now more than 5000 women have been enrolled, and half have had already their data analyzed. Of these approximately half of whom have had MRI and the other have not had MRI. Since MIPA is not an RCT, the two groups, i.e. with or without MRI, are not homogeneous — understandably the group receiving MRI included, on average, younger women and those with denser breasts compared to the women who did not receive MRI.

Notwithstanding these reservations, one of the most important findings of the MIPA study at this stage is already becoming clear, namely that, considering those women who finally had breast conserving surgery (BCS) treatment after MRI, 73% had that treatment unchanged by MRI, 13% had a less extensive BCS compared to that planned before MRI, and 14% had more extensive BCS compared to that planned before MRI. Thus, BCS was tailored, personalized to the disease extent.

"...mastectomy prompts MRI, not vice versa...."

In terms of surgery actually carried out, there were significantly more mastectomies (21%) in the MRI group compared to 16.0 % in the non-MRI group. However, this difference is NOT due to the use of MRI, but mainly due to the differences in patient selection.

CONCLUSION

The principal findings of the MIPA study are shown in the diagram above, with the clear main message so far being:

Pre-planning of a mastectomy based on mammography/ultrasound prompts an MRI scan (frequently requested specifically by a surgeon who wants the assurance of MRI prior to carrying out the surgery). — the MRI scan does not result in the carrying out of more mastectomies. On the contrary, mastectomy prompts MRI, not vice versa.

Gadolinium retention — impact on breast MRI

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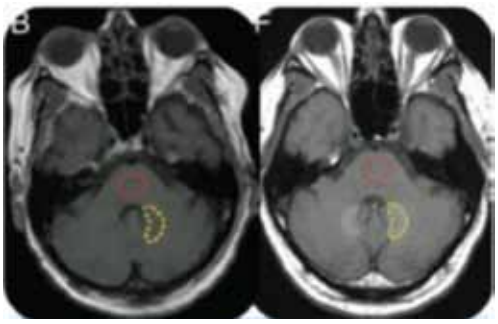
The objectives of Prof. Barkhausen's presentation were clear — to review the basic need for contrast media in breast MRI and then review the current status and clinical data regarding gadolinium deposition, the current regulatory recommendations and the specific impact on breast MRI.

Regarding breast MRI, the relatively recent introduction of diffusion weighted imaging (DWI) has shown potential for the detection and characterization of cancer although some issues related to image quality can limit the more widespread use of the technique. Nevertheless the potential benefits of the technique are the differentiation of benign and malignant lesions; the assessment and prediction of therapeutic efficacy and — perhaps— the non-contrast -detection of breast cancer. Despite these advantages there are many cases where the identification of lesions using DWI is however much more difficult than with Dynamic Contrast Enhancement. Direct comparison of DWI and DCE in breast cancer was carried out in a recent meta-analysis of 14 clinical studies, with the result showing that DCE had a higher sensitivity than DWI (93% vs 85% respectively), although specificity was slightly lower (72% vs 76 % respectively).

Thus while DWI is an exciting new technique with promising potential, contrast media is currently still needed for breast MRI.

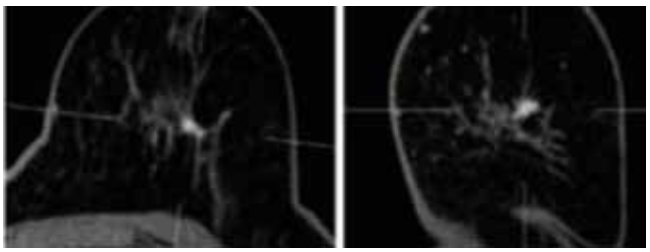
Adverse events of MRI contrast media



In patients who had received multiple administrations of (mostly linear) GBCAs, depositions of Gadolinium have been found in the dentate nucleus region of the brain. So far, no adverse events associated with this have been reported

In general MR contrast agents have excellent safety profiles although in 2006, cases of a new condition, known as Nephrogenic Systemic Fibroses (NSF) were identified as being associated with the administration of gadolinium-based contrast agents (GBCA) , particularly in patients with poor renal function. The European regulatory authorities (EMA) issued an advisory notice classifying the GBCA into low, medium and high risk categories. Use of low risk GBCAs and ensuring that the patient receiving the GBCA had normal renal function has basically resulted in the effective disappearance of NSF.

However in 2014 a potential new problem was identified when an intense signal was observed in the dentate nucleus in the brains of patients who had previously received GBCAs. The implication that this signal was the result of gadolinium from the previous GBCAs somehow remaining deposited in the brain. Since this initial observation there have been many publications confirming and expanding the original findings. The overall conclusions are that the observed signals are indeed due to the prior use of GBCAs, with mass spectrometry analysis of autopsy samples confirming that gadolinum was present in the dentate nucleus and that the amount of gadolinium deposited in the brain correlated with the total amount of gadolinium given in the previous GBCA administrations. Since GBCAs are known not to pass the blood-brain barrier, it was speculated that gadolinium may be being released from the chelating molecule in which it is formulated. Laboratory trans metallation tests confirmed that Gd could indeed be released from its chelate, with significant differences being observed in the



The benefits of contrast enhanced MRI in breast imaging. The above case is 53 yr old woman, with BIRADS 4 on mammography but a negative stereotactic biopsy. Contrast enhanced MRI (images above) clearly show the lesion; MRI-guidance for a second biopsy would clarify the case

stability of the different chemical structures. Thus multi-purpose linear chelates, e.g. Magnevist and MultiHance showed significant deposition of Gd ions whereas macrocyclic compounds such as Dotarem and Gadovist showed no deposition of Gd. However animal studies have shown the presence of minimal amounts of Gd in the brain with all tested GBCAs.
It should be noted that so far there have been no reports of any adverse reaction in patients with Gd deposited in their brain.

Breast MRI

There are several excellent indications for the use of contrast media in breast MRI, but the majority of patients only need one or two contrast enhanced breast MRI examinations. In the light of this it is recommended that any patient with a need for contrast enhanced breast MRI should receive the exam. However the situation is slightly more complex in a more difficult population of patients, e.g. the repeated screening of high risk patients, e.g. BRCA patients. In such cases individual risk/benefit analyses should be established. For this it is necessary to be able to quantitate the benefit of MRI in screening high risk patients. Recently an extensive meta-analysis covering more than 1950 patients showed that the use of MRI yielded significantly higher sensitivity and specificity than mammography alone. This position reflected in several regulatory guidelines, such as the NICE guidelines in the UK which recommend that annual MRI surveillance should be offered to high-risk women such as those with a BRCA mutation. However such guidelines (so far) do not address the question of Gd deposition so Dr Barkhausen's recommendations are based on his own experience. These are that

1) In Contrast Enhanced Breast MRI there are more benefits than risks — cancers can be missed without MRI
2) Written informed consent should be recorded including reference to Gd deposition
3) Macrocyclic GBCAs should be used where possible
4) However the carrying out of contrast enhanced MRM should NOT be stopped

Note added in proof

Since Prof Barkhausen's presentation at the Breast Care Day, the Pharmacovigilance and Risk Assessment Committee (PRAC) of the European Medicines Agency has issued a preliminary assessment of Gd contrast agents and recommended regulatory actions including suspension of the market authorisation for some linear GBCAs Full details of PRAC position available DI Europe May 2017 p 35

Is tomosynthesis ready for use in mammography screening?

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Prof. Heywang-Köbrunner started off with a reminder of the values of mammography screening, which so far is the only method with a proven effect on mortality reduction and proven to be appropriate for mass screening. Nevertheless there are some drawbacks to the technology, such as the possibility that an early diagnosis of a slow-growing tumor may in fact represent overdiagnosis. There is also the risk of false positives, not to mention that the late detection of some tumors may be too late for adequate intervention.
The relatively recent technique of digital breast tomosynthesis (DBT) is attracting a lot of interest with its excellent sensitivity and good specificity. Despite this no organized screening program with DBT has yet been set up although several large studies of DBT have been carried out. In America such studies are retrospective whereas the European studies are generally prospective and differ in several respects from those in America. In Europe highly trained readers are used; double reading is carried out and screening is on a bi-annual basis. All the American studies show that the sensitivity of mammography screening can be increased significantly (on average by 27 %) by the addition of DBT and that there is a slightly lower recall rate. The main drawback of these trials is that by combining FFDM with DBT the patient has a double exposure of ionizing radiation, which would not be acceptable in Europe for screening.

			Detection rate/1000			recall-rate		
Trial	number	single/ double r.	FFDM	FFDM+TS	difference	FFDM	FFDM+TS	difference
Malmoe	7500	d	6,3	8,9	plus 43%	2,6%	3,8%	plus 43%
STORM 2 s2D/DBT	9677	d	6,3	8,8	plus 39%	3,4%	4,5%	plus 32%
ALL	17177	d	6,3	8,8	plus 40,4%	3,1%	4,2%	plus 37,50%

Comparison of the two most recent European studies of tomosynthesis. Although there were differences in study design and in methodology, both the Malmö and STORM2 trials reported significant increases in the cancer detection, albeit with increases in recall rate

In Europe the first prospective DBT studies also looked at the effect of adding DBT to FFDM and showed even greater increase in sensitivity although there were variable effects on the recall rate. It should be noted that, perhaps due to the practice of double reading in Europe the recall rate is anyway considerably lower than that in the States. Later trials in Europe used different protocols to look at tomo alone vs DM alone. The Malmö trial used Siemens

mammography system to compare wide-angle tomo (without a synthetic 2D view) directly with DM. In the Malmö trial there was no increase in radiation dose in the tomosynthesis arm of the study compared to FFDM, since in the tomo arm only one view (MLO) was taken as opposed to the two-view (CC and MLO). In fact there was even a small reduction in dose.

The results showed that the cancer detection rate was 43% higher than that of DM alone but there was also an increase in the recall rate. The STORM-2 trial showed that, compared to a combination of DBT + DM, the combination of DBT plus a synthetic 2D image gave an equivalent increase in cancer detection rate (39%), but of course without the additional radiation dose caused by the DM. However the recall rate was significantly increased.

Overall these recent European results confirm that the increased cancer detection rate of DBT can be achieved without the need for a DM scan. There is a moderate increase in recall rate.

A remaining challenge is however the significance of the increased rate of detection of cancerous lesions and whether this could simply be overdiagnosis. This aspect is partly addressed via analysis of interval cancer rates. The preliminary data from the European trials are relatively encouraging in this context. However the recent data on interval cancers from the US trials (all retrospective) are a bit worrying in that the increase of detection rate of cancers is approximately ten times that of the decrease in interval cancers. More information is needed on interval cancer rates and stage distribution in follow-up rounds.

Conclusion

• DBT has significant advantages over DM and is more promising for mass screening than US or MRI

• Approval of DBT will however require more data on interval cancer rates.

• More time will be needed for optimization of logistics, reader training, dealing with the question of extra time needed for reading tomo images and for carrying out focussed research on these issues

The Malmö Breast Tomosynthesis Screening trial

Dr Lång described the basic aim of the Malmö trial which was to study the accuracy of a one-view wide-angle Digital Breast Tomosynthesis (DBT) compared to two-view Digital mammography (DM) in population-based screening.

In the trial, the Siemens Mammomat Inspiration system was used for both DBT and DM. With this system the absorbed dose in one-view (MLO) DBT is actually less (1.6mGy) than that of two-view DM.

The prospective, population-based study involved approximately 15000 women randomly taken from the screening population in Malmö, Sweden where women are screened starting from 40 years of age. All women underwent DBT and DM and the images were read by independent double readers. The reading work flow is shown below. Interim results have already been published. The data from 7500 women showed that in the DBT arm of the trial, the recall rate was 3.8% whereas in the DM arm, 2.6% were recalled. Thus there was a 43% increase in the DBT recall rate compared to that in DM. but it shouldn't be forgotten that there was a 43% increase in the detected cancers with DBT compared to DM so in this context the recall rates are acceptable.

From the trial several conclusions can be drawn

1) Tomosynthesis increases breast cancer detection in screening. Although there are several differences in the design and technology of other European prospective population-based trials (e.g. the others used Hologic systems whereas the Malmö trial used Siemens Mammomat systems) they all showed increased cancer detection rates

2) Tomosynthesis detects small invasive cancers.

3) There is an increase in recall rates using DBT, when starting from a low base-line. This is mainly due to the higher detection rate but also to a slight increase of false positives.

4) There is a slight change in the false positive panorama

5) One-size fits all — DBT finds additional cancers in both dense and non-dense breasts

6) One-view wide-angle tomosynthesis is sufficient

7) Breast compression can be reduced

8) There will be workflow challenges arising from the longer reading times in DBT. The development of software based on artifical intelligence algorithms however is showing great promise in increasing the efficiency of reading

9) The interval cancer rates needs further investigation.

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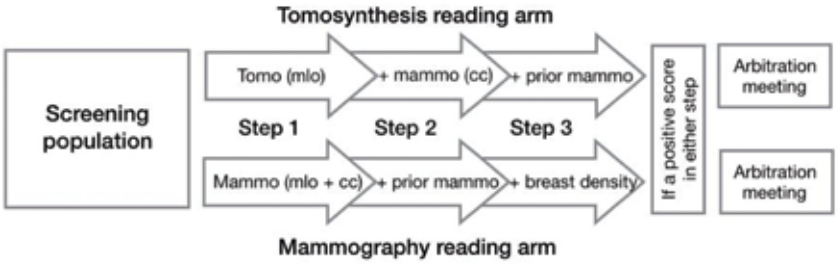

Design of the Malmö trial

Summary

• Breast tomosynthesis increases the cancer detection rate with a reasonable elevation of the recall rate.

• Once the question of interval cancer rates has been further investigated, tomosynthesis should be used in screening mode, with artificial intelligence-based systems being used to alleviate the longer reading time required with DBT.