Focus on Dynamic Contrast-enhanced in Breast Cancer

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The analysis of breast tissues was related to the origins of medical use of nuclear magnetic resonance (NMR) since Damadian's experiments during the Seventies of the last century [1]. However, clinical breast magnetic resonance imaging (MRI) studies using standard T1-, proton density-, and T2- weighted sequences were disappointing.

A dramatic change was obtained in 1986, when S.H. Heywang firstly obtained contrast-enhanced (CE) MR images after intravenous administration of gadopentetate dimeglumine (Gd-DTPA) [2]. The availability of faster T1-weighted gradient-echo spoiled sequences allowed for dynamic imaging, permitting the combination of morphologic and dynamic parameters, the latter classified by C.K. Kuhl in 1999 [3] as continuous increase (type 1), plateau (type 2), and washout (type 3). Two ways for breast MRI were followed on the two sides of Atlantic Ocean during about 15 years: 1) in Europe, dynamic CE imaging with 60-90-s temporal resolution and a relatively lower spatial resolution, preferentially using axial or coronal planes; 2) in the United States, non-dynamic CE fat-saturated imaging with high spatial resolution and low temporal resolution, preferentially using sagittal planes. Thereafter, these two ways were substantially unified by protocols which permit both high spatial resolution and sufficient temporal resolution (up to 120 s), with or without fat-saturation (axial or sagittal currently preferred to coronal planes). On the other hand, clinical research studies on single-voxel proton MR spectroscopy (MRS) were performed using the choline peak as a marker of malignancy [4], while during the Nineties MR-guided breast needle biopsy became available, finally filling a relevant gap for a breast imaging modality in clinical practice [5]. In 2003, the American College of Radiology extended to MRI the Breast Imaging and Reporting Data System (BI-RADS) [6], promoting a standardization of lexicon and interpretation, including the classification into the three types of dynamic curves. Thus, dynamic CE MRI has been included in the standardized interpretation of breast MRI, at least in terms of qualitative visual evaluation

Afterwards, especially in the last decade, technical developments such as strong and rapid field gradients, multichannel dedicated coils and parallel imaging, high-field (3T) magnets, new dedicated sequences, including those for diffusion-weighted imaging and 2D/3D multi-voxel proton MRS, made breast MRI technology more and more robust and attractive in terms of multiple options offered to clinicians and researchers. However, dynamic CE MRI remains as the standard of care when an MRI study of the breast has to be performed with the only exception of the evaluation of breast implant integrity.

Notwithstanding a growing evidence for a high diagnostic performance of dynamic CE breast MRI, including high sensitivity not only for invasive cancers but also for ductal carcinoma in situ, a long-standing false "mantra", frequently repeated also by breast radiologists, acted against its clinical use: "Breast MRI is a diagnostic tool with high sensitivity but with low specificity". This affirmation implied a large number of MRI false positives and strongly limited the potential application of this technique to a screening setting, due to a great fear of a deluge of "recalls", i.e. of cases of healthy women requiring further investigations. In 2008, the large meta-analysis by Peters et al (also including many old studies performed with today outdated, non-dynamic, technical protocols) stopped this discussion: 90% sensitivity and 72% specificity [7]. As a matter of fact, when breast MRI was applied to high-risk screening, sensitivity was over 90%, specificity went up to 97%, and the positive predictive value (62%) was not significantly different than that of mammography or ultrasound [8]. However, we should always consider that the diagnostic performance of whatever test depends on many factors other than technical quality and readers' experience and skill, especially including patient selection and clinical setting. Last but not least, new contrast materials, different from those traditionally used due to a higher T1-relaxivity and/or concentration, are now entering dynamic CE breast MRI with promising results in terms of a higher diagnostic performance [9, 10].

A large debate among breast cancer specialists is open on indications for dynamic CE breast MRI [11]. Some indications are now accepted: high-risk screening, carcinoma unknown primary, breast implant integrity evaluation (using unenhanced specialized sequences), evaluation of the effect of neoadjuvant chemotherapy (NAC), and evaluation of suspected recurrence when conventional imaging is inconclusive and needle tissue sampling cannot be performed. Other indications, especially preoperative MRI, are under discussion [11-13]. New indications such as nipple discharge [14] and evaluation of lesions with uncertain malignant potential at mammography- or US-guided

needle biopsy (B3 lesions) [15] are now emerging. Research topics such as breast vascularity at dynamic CE-MRI are under investigation [16-21]. Notably, the breast cancer medical community needs high-quality research and standardization of methods for dynamic CE breast MRI. Also for accepted indications such as is the NAC setting, recent systematic reviews [22-24] reported heterogeneity across MRI parameters and outcome definition (including pathological response) but confirmed that dynamic CE breast MRI is the best approach for evaluating the effect of NAC either during or after NAC.

While future directions are already proposed in terms of technical developments such as diffusion tensor imaging or MRI/PET fusion, a new change of paradigm is behind the corner: breast MRI from diagnosis to prognosis, exploiting in particular the information available from quantitative dynamic analysis of contrast uptake and washout [25-28]. This last ability to work as a prognostic tool may play in favor of dynamic breast MRI as a way for an in-vivo insight into breast tumor biology, potentially overcoming the controversy on preoperative breast MRI. Finally, new perspectives for dynamic CE MRI of the breasts are open for the study of background parenchymal enhancement, especially in correlation with mammographic density and breast cancer risk [29].

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