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Dynamic MR imaging as a predictor of prognosis in breast cancer

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Abstract. Contrast-enhanced MR imaging (CE-MRI) has become a widely accepted complementary method for diagnosing breast cancer. It has been suggested for evaluating patients with breast implants, patients at risk of tumour multifocality or recurrence, search for occult primary cancer in presence of axillary metastasis and monitoring the effect of preoperative chemotherapy. The clinical usefulness of MR imaging in patients with increased genetic risk of breast cancer is still under investigation. There is scientific evidence to support the hypothesis that CE-MRI may carry the prognostic significance of angiogenesis, and one of the future indications of this method can be the prognostic evaluation of breast cancer patients by the functional mapping of the angiogenic activity of tumours. On the basis of the promising results of recent reports, further large-scale studies are needed to evaluate the impact of MR parameters on long term overall survival of patients with breast cancer.

1. Clinical applications of MRI in breast cancer

Although, mammography and ultrasound (US) remain the first line imaging methods, additional techniques may help either in the diagnosis or in the clinical management of breast cancer patients. For diagnosing breast cancer, magnetic resonance imaging (MRI) has emerged as the most sensitive complementary tool [1]. However, in spite of the fact that there are numerous approaches in use at different institutions, the protocols for contrast-enhanced MRI (CE-MRI) seem to be converging, and agreement exists on the clinical indications, as well.

Most frequently, MRI is used to examine patients who had breast augmentation or reconstruction surgery [2,3]. In these cases, breast implant failure or tumour recurrence is hard to or cannot at all be detected by conventional techniques. Non-contrast MRI is the appropriate method to check the implant integrity, but in all other indications, the intravenous administration of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) is necessary for the visualization of neoplastic tissue [4]. Due to the very high sensitivity of CE-MRI in diagnosing breast cancer, initially it was treated as a problem-solving complementary modality to the routine diagnostic work-up, especially for further evaluation of suspicious lesions found at physical examination or mammography. According to a recent large multi-centre study, in most cases breast biopsy cannot be avoided with the use of MRI [5]. There is no scientific evidence to support that MRI could reduce the number of unnecessary breast biopsies in this patient group. CE-MRI is indicated in the following clinical situations:

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1. Clinical staging before breast conservation surgery

Since small or unifocal breast malignancies can be treated with a less radical surgical method, and mastectomy is the choice for extensive disease, preoperative assessment of multifocality, multicentricity and accurate report on tumour extent are of great importance in planning breast surgery [6,7]. CE-MRI is found to be more precise in measuring tumour size and extent compared to conventional methods [8]. The clinical management of breast cancer patients can be changed in 15–20% with the use of MRI [9].

2. Imaging after breast conservation/reconstruction surgery

Although, local recurrence is expected to occur in 1–2% of cases per year [10], post-treatment scarring may impair the detectability of recurrent or residual tumours. In clinically suspicious cases, CE-MRI can distinguish enhancing malignant tissue from benign type scarring or fibrosis [11]. The only disadvantage of CE-MRI is that post-irradiated inflammatory changes also show moderate contrast enhancement, therefore MRI is not indicated during the first 12 months after surgery, and 18 months after radiation therapy [12]. Although, according to a recent study, radiation-induced changes occur only in the first 3 months after therapy, and with more refined diagnostic criteria can be differentiated from tumour recurrence [13]. Patients treated with reconstruction surgery (using breast implants) are also candidates for CE-MRI during the postoperative follow-up [14].

3. Detection of occult breast carcinoma

Especially in mammographically dense breasts, conventional imaging techniques are unable to detect the primary focus of a clinically evident metastatic carcinoma. In this carcinoma unknown primary (CUP) syndrome we can utilize the high sensitivity of CE-MRI for identifying the primary source of the disease [15,16].

4. Monitoring the effect of neoadjuvant chemotherapy

In advanced stages of breast cancer, there is often a need for preoperative chemotherapy in order to improve the overall survival of patients. Neoadjuvant therapy has the advantage of providing tumour shrinkage and it is the earliest treatment against micrometastases. Successful preoperative chemotherapy can make possible breast conserving surgery, as well [17]. CE-MRI is good at monitoring the angiogenic activity of tumours, thus is capable of mapping the viable areas of lesions. With this method the response to the chemotherapeutic agents can be assessed even in the early stage of the therapy [18,19].

5. Screening of patients with the risk of hereditary breast cancer

The group of patients at high-risk of breast cancer includes those women who had a contralateral breast cancer, factors that indicate genetic predisposition (family history, BRCA1 and BRCA2 genes), previously treated Hodgkin's disease or previously diagnosed in situ cancers or atypia in the breast. Other factors like patient's age, age at first birth and race are also of importance for the evaluation of risk. In this patient group (which usually represents a younger population) CE-MRI would be preferable over mammography because of its higher sensitivity [20–22], and no radiation when repeated examinations have to be performed in young women.

6. Other indications and considerations

If a non-palpable suspicious lesion is visible at CE-MRI alone, and is not detectable on X-ray or US, biopsy should be performed by the guidance of MRI. There have been many reports on describing MR-guided biopsy and localization techniques [23,24], but its acceptance into common clinical use is limited. Since spatial and temporal resolution of CE-MRI is improved considerably, the group of *in situ* carcinomas, is better visualized now with newer techniques [25]. Future application of CE-MRI can be the assessment of extensive ductal carcinoma *in situ* (DCIS) [26]. In the past, another limitation of

CE-MRI was the reported poor detectability of invasive lobular cancers, which has also been improved. High resolution CE-MRI is indicated for clinical staging, when there is a suspicion of lobular cancer [25].

CE-MRI is increasingly being used as a complementary modality to conventional diagnostic imaging methods to examine breast cancer patients. However, CE-MRI has very high sensitivity in detecting breast malignancy, its relatively low specificity still a known limitation. There have been numerous attempts to improve the diagnostic accuracy of breast MRI. Among these, magnetic resonance spectroscopy (MRS) appears to be the most promising approach [27]. Several studies using hydrogen (^{1}H) MRS showed that malignant lesions could be differentiated from benign and normal breast tissues based on the production of choline-containing compounds (tCho). However, underlying biochemical mechanisms are not fully clarified, according to the working hypothesis, increased tCho concentration is probably a sign of cell proliferation in malignant tissues. Since benign proliferative lesions can also produce considerable amount of tCho, ^{1}H-MRS detected tCho is apparently not a fully specific marker of breast malignancy. Recent reports showed that adding ^{1}H-MRS could improve the diagnostic accuracy of CE-MRI. In one study, CE-MRI alone had a sensitivity of 100% and specificity of 62.5%. With the addition of ^{1}H-MRS, specificity increased to 87.5% [28]. According to another study, which was an observer performance study, after the addition of ^{1}H-MRS, all observers achieved significantly higher diagnostic accuracy, and there was an increase in inter-observer agreement, as well [29].

2. Prognostic factors in breast cancer

Survival of patients diagnosed with primary breast cancer is largely determined by conventional prognostic factors including the presence of metastatic axillary lymph nodes and size of the tumour. Nodal status is not only a time-dependent staging variable, but also serves as a marker for tumour aggressiveness [30]. Tumour size is another factor that has long been recognized as an important predictor of disease outcome in breast cancer patients [31], furthermore, the risk of death could accurately be estimated with combined information on the size and number of involved nodes [32]. Patients could be grouped into different prognostic groups according to histological type of the tumour. Tubular, invasive cribriform and mucinous carcinomas have favourable prognosis. Medullary, papillary and classical lobular breast cancers represent a group of tumours with good and moderate prognosis, and the worst clinical outcome is associated with invasive carcinoma of no special type [33]. Histological grading according to the Elston–Ellis classification taking into consideration the combination of tubular formation, nuclear pleomorphism and mitotic rate highly correlates with long-term survival; the lower grade is associated with better prognosis [34]. In the routine clinical practice, the use of stage related as well as biological factors is needed for predicting prognosis. The Nottingham prognostic index, which based on the pathological tumour size, lymph node stage and histological grade is one approach to fulfil this need [35].

Ki-67 is an excellent molecular marker of cell proliferation and proved to be a powerful and independent prognostic factor for node-negative patients. Because of the technical difficulties in measuring this factor, the ki-67 labelling index is still not widely used in routine clinical work [36]. Estrogen and progesterone receptor status in breast cancer is currently used to select patients for hormonal therapy, but can also provide prognostic information [37]. The oncogene c-erbB-2 (HER2/neu) has predictive value for response to herceptin (a monoclonal antibody against HER2 receptor) [38]. It is unquestionable that hormone receptor and c-erbB-2 status correlate with clinical outcome, but their role in predicting

prognosis in node negative patients remains controversial [39]. Other molecular markers are also under investigation, such as growth factor receptors, p53, DNA ploidy, S-phase fraction, cathepsin-D, and E-cadherin. Although, these molecular factors have prognostic significance at univariate analyses, the best prognostic indicators remain the clinically used traditional histomorphological factors [34].

3. Angiogenesis and CE-MRI

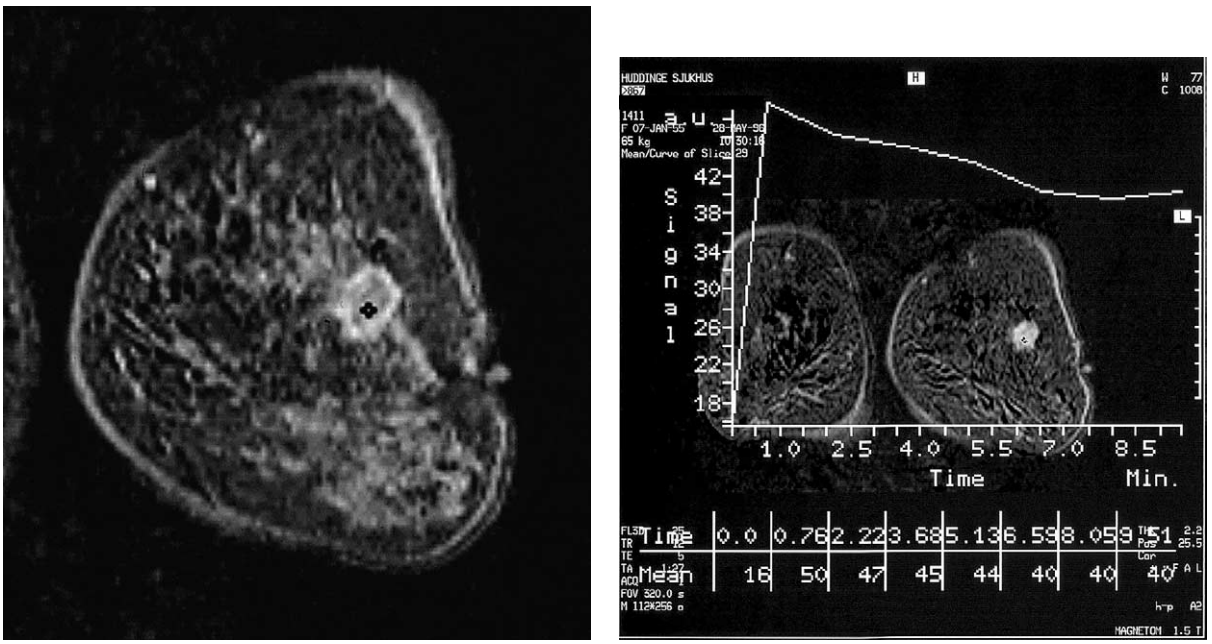
The term angiogenesis was introduced by Folkman [40] that describes the process of new formation of vessels from pre-existing vasculature. Growth, invasion and metastatic activity of different malignant tumours are highly dependent on angiogenesis. The degree of intratumoral microvessel density (MVD) was first proposed as a measure of angiogenic activity of breast carcinomas [41]. To date a number of studies have demonstrated that there is a strong association between increased MVD and decreased disease free and overall survival and MVD is proved to be an independent prognostic factor in patients with breast cancer [41–44]. These studies suggest that highly vascularized tumours have higher metastatic capacity and are associated with poorer prognosis. Other studies, however, could not confirm these findings [45,46]. These contradictory results can partly be explained by the variability in selection of endothelial antibodies, methods for counting microvessels, and different interpretations of findings [47]. In addition, vascular heterogeneity of tumours may also influence the measurement of vascular density [48,49].

Although, several factors are involved, endothelial growth factor (VEGF) remains the major regulator of angiogenesis. This angiogenic factor is the most important marker of endothelial cell proliferation and vascular permeability. VEGF regulates the neovascularization of physiological processes, such as wound healing, changes associated to menstrual cycle, but in malignant tissues the expression of this cytokine becomes uncontrolled. With regard to prognosis, it has also been proved that higher expression of VEGF is associated to shorter disease free interval and survival in breast cancer patients [50].

Angiogenesis of invasive breast tumours has been shown to be one of the main factors that affect MR contrast agent uptake. MR contrast enhancement is dependent on certain physiologic properties of vessels: besides perfusion and blood volume, which is mainly, related to MVD, endothelial permeability is also of importance. It is apparent that highly permeable blood vessels of malignant tissue allow the higher diffusion rate of a MR contrast agent through the capillary wall, producing stronger extravasation and increase in signal intensity. Some studies have pointed out a correlation between tumour enhancement and MVD [51–53], while others have reported no such relationship [54,55]. There is a recent study that may give an explanation to this controversy. Knopp and colleagues found a strong correlation between MR contrast kinetics and VEGF expression [56]. According to their results, VEGF-induced vascular permeability plays a dominant role in MR contrast dynamics, and the effect of vascular density seems to be inferior.

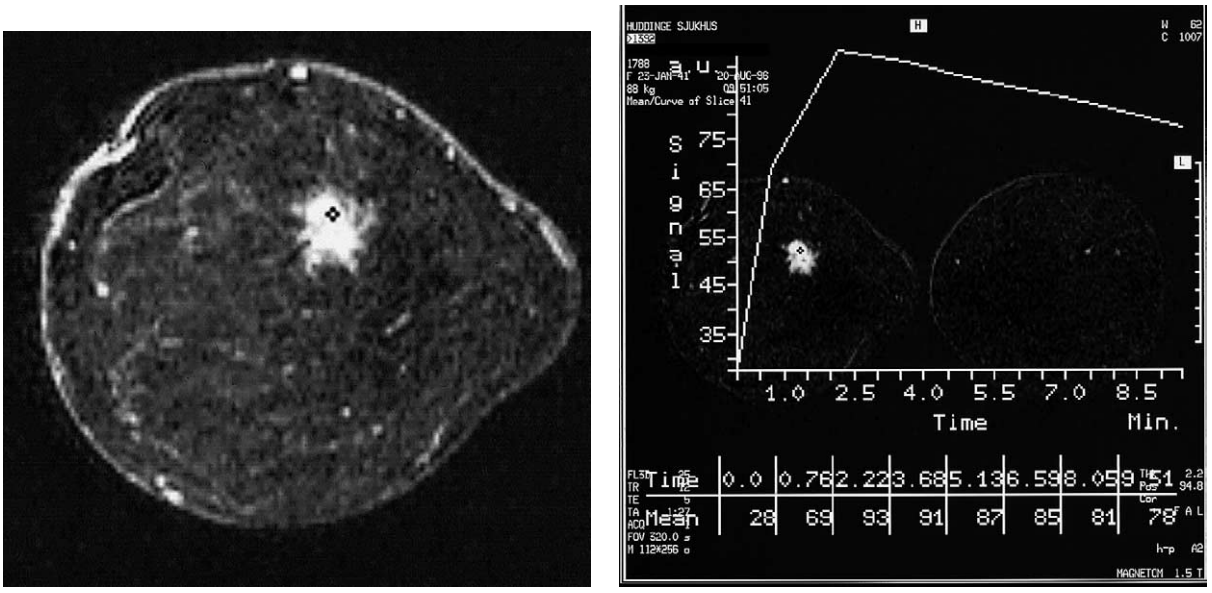
4. CE-MRI in predicting prognosis

The prognostic significance of angiogenesis in breast cancer has been repeatedly shown [41–44], while some studies do not support these findings [45,46]. A relationship between angiogenesis and MR contrast enhancement has also been demonstrated [51–53]. As contrast enhancement patterns (both morphologic and kinetic) are linked to the vascular properties of tumours, these MR features might be useful for *in vivo* tumour grading, assessing metastatic activity and predicting prognosis in breast cancer.



(a) (b)

Fig. 1. Coronal T1-weighted 3D fast low angle shot (FLASH) subtracted images of a 41-year-old woman with a histopathologically proved 22 mm high grade invasive ductal carcinoma with associated ductal carcinoma *in situ* (DCIS) in her left breast showing rim-enhancement (a) and washout type enhancement curve (b).



(a) (b)

Fig. 2. Typical morphologic and kinetic features of malignancy are demonstrated on coronal T1-weighted FLASH subtracted MR images: spiculated irregular outlines (a) and washout type time-signal intensity curve (b). The subject was a 55-year-old woman with a histopathologically proved 2 cm large invasive ductal carcinoma in her left breast.

A number of studies examined the hypothesis that kinetic MR parameters derived from time–signal intensity curves are related to established prognostic factors and therefore can also be used for predicting the outcome of the disease. Boné et al. [57] compared different classical prognostic factors and molecular markers with MR contrast enhancement in a population of 50 patients with breast cancer using semi-dynamic MR technique, and found that contrast enhancement ratio was associated with histological malignancy grade and tumour proliferation. They also reported a correlation between washout and tumour grade. Our research group confirmed these findings with using standard dynamic MR technique and multivariate statistical analysis of 61 invasive malignant breast lesions [58], and pointed out that time-to-peak enhancement was independently associated with histological grade and steroid receptor status, and there was a correlation between qualitative variable "curve type" and cell proliferation as reflected by ki-67. Mussurakis et al. [59] also found a relationship between contrast enhancement and prognostic factors. In their study, increased enhancement ratio was associated with higher histological grade and presence of metastatic nodes in 53 women. In a more recent study, Komatsu et al. reported that malignant type time–signal intensity curves were found more frequently in lymphatic invasion and lymph node metastasis investigating 69 malignant breast lesions and proposed dynamic MR technique for the prediction of lymph node metastasis [60]. Tuncbilek and colleagues published a study on 55 patients with invasive breast cancer, and found that MR enhancement parameters significantly associated with histological grade and lymph node status [61]. In another study, Oshida et al. investigated ductal carcinomas *in situ* (DCIS) and compared pharmacokinetic MR parameters to histological findings [62]. They reported on an association between MR parameters and histologic grade using 39 subjects, and again proposed functional MRI as a prediction tool for breast cancer. Although, the results of the above mentioned publications appear to be consistent, we have to mention two other studies [63,64], where no correlation was found between the degree of MR enhancement and prognostic factors. The source of these contradictory findings remains unknown, however, there are several possible influential factors including the method of defining region of interests (ROI), variability in calculating contrast enhancement parameters, and using different MR techniques [65].

Our research group found that rim enhancement could be one of the morphological MR patterns that may be of prognostic relevance [58]. The presence of this sign showed strong association with higher histological grade and negative ER status, and also with ki-67 status, although this was only marginally significant. Multivariate analysis confirmed these correlations. Peripheral rim enhancement pattern is an important morphologic sign in the differential diagnosis of breast masses [66]. Presence of this architectural feature has approximately 79–92% predictive value for breast malignancy [67]. It was also reported to be associated with high degree of angiogenesis in the tumour periphery [52,53], but central tumour necrosis also accounted for this feature and may even be more pronounced than MVD [68]. One study showed a correlation between rim enhancement and high DNA S-phase percentage and suggested that rim enhancement is more often seen among rapidly growing cancers [69]. Although, rim-enhancement was in the focus of several investigations, other studies showed that other architectural MR features might also be of importance in prognosis determination. Besides rim enhancement, spicula formation, serrated borders and linear enhancement patterns were highly associated to different histological subtypes of invasive breast cancer and it was suggested that CE-MRI may be a useful tool for estimating breast cancer prognosis [70,71].

Due to the relatively longer median survival time of patients with breast cancer, most of the studies investigating the prognostic relevance of CE-MRI focused on the correlation of MR features with known prognostic factors. For a newly proposed prognostic factor it is, however, a key issue whether there is a direct association with disease free or overall survival of patients during the follow-up period. On the

other hand, a comparison has to be made with other established prognostic factors to test for statistical independence. In malignancies other than breast cancer, it has been shown that dynamic MR parameters are able to provide valuable prognostic information. In one study, pharmacokinetic MR parameters were found to be independent predictors of disease free survival in paediatric osteosarcoma [72]. It has also been repeatedly shown that CE-MRI is able to asses tumour aggressiveness and provides information on the risk of local recurrence and on the prediction of treatment success in cervical cancer [73,74]. A recent study by Fujimoto et al., involving 94 patients with small peripheral lung cancers, compared dynamic MR features with tumour vascularity and overall survival [75], and showed a significant association between the slope of the enhancement curve and disease outcome. In breast cancer, to our best knowledge, the first survival analysis on kinetic MR parameters was published by our research group [76]. This study was carried out on a population of 50 patients with breast cancer, and the relation of semi-dynamic MR parameters to disease free and overall survival was investigated with a median follow-up of 95 months for surviving patients. MR enhancement was found to be an independent prognostic factor for disease-free survival after the comparison with other prognostic factors in multivariate analysis. Despite the long follow-up period, relatively small sample size was a certain limitation of this study.

In summary, there is scientific evidence to support the hypothesis that CE-MRI may carry the prognostic significance of angiogenesis, and one of the future indications of CE-MRI can be the prognostic evaluation of breast cancer patients by the functional mapping of the angiogenic activity of tumours. On the basis of the promising results of recent reports, further large-scale studies are needed to evaluate the impact of MR parameters on long term overall survival of patients with breast cancer. Kinetic and morphologic MR features should be examined and compared to existing prognostic factors of invasive and in situ breast cancers.

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