Current and Future Applications of Magnetic Resonance Imaging (MRI) to Breast and Ovarian Cancer Patient Management

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Magnetic resonance imaging (MRI) is occupying an increasing niche in the clinical diagnostic workup of several cancers, including breast cancers. Despite the high level of implementation of mammography, it has become apparent that MRI can play at least a complementary role in the imaging and diagnosis of primary breast cancers, including ductal carcinoma in situ, the earliest stage of breast cancer that is associated with an increased risk of invasive breast cancer. This can also be said of inflammatory breast cancer, of low incidence but with high impact on overall breast cancer mortality rates, and for which mammography is not ideal due to the typically diffused nature of this disease. Much of the value of breast MRI is dependent on its high sensitivity, resulting from the use of contrast agent enhancement in the detection of breast cancer. Interest has also increased in the application of diffusion-weighted MRI for early assessment of treatment response in this disease. Regarding ovarian and other gynecological cancers, MRI has already demonstrated value in the evaluation of patients with ovarian masses, uterine leiomyoma, endometrioma, and cervical cancer. Features on MRI suggestive of malignant ovarian tumors are varied, and span irregular or solid components to a cystic mass, prominent septations, evidence of peritoneal, hematogenous, or lymphatic spread, or local invasion. The majority of ovarian malignancies are diagnosed in advanced, incurable stages, where exploratory laparotomy provides the opportunity for maximal debulking. Although a role for MRI has yet to be established in this initial setting or in staging, some studies have shown that high sensitivity may be achieved with contrast agent-enhanced MRI for detection of recurrent disease, including demonstration of macroscopic intra-abdominal dissemination and the hallmark omental "cake". Efforts in recent years have been focused on design of MRI contrast agents (MRI-CAs), which either target biomarkers, or take advantage of the different physiology of cancerous cells. MRI-CAs based on gadolinium complexes, ferrumoxides, or other metallic nanoparticles have been investigated. This review will focus on the recent progress in the application of MRI to the imaging of breast and ovarian cancers, and present a possible role for molecularly-targeted contrast agents in enriching the context for MRI-based diagnosis. [*P R Health Sci J 2010;3:223-231*]

Key words: Magnetic Resonance Imaging, Breast Cancer, Ovarian Cancer, Contrast Agents

MRI and Breast Cancer Management

The guidelines for application of diagnostic imaging, and MRI in particular, to breast cancer patient evaluation and management continue to evolve, and some are articulated by the National Comprehensive Cancer Network (NCCN; 1). Currently, the breast cancer patient populations who might benefit most from pre-operative MRI include genetically-defined high-risk patients, those with dense breasts as determined by mammography, those with a lobular invasive

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cancer, a multi-centric tumor or a previously-diagnosed bilateral tumor, those with significant distinctions in size between mammography and ultrasound (US) findings, or those for whom partial breast irradiation or other breast conserving therapy is being considered (2-5). Despite this extensive experience, considerable controversies exist as to the true benefits of the application of MRI to treatment management.

A retrospective review of patients with newly diagnosed breast carcinoma who had MRIs prior to surgery noted 381 lesions in 361 patients with pathologic confirmation of ductal carcinoma *in situ* (DCIS), invasive carcinoma, or mixed DCIS and invasive carcinoma (6). Of these lesions, 16.8% were DCIS, 26.5% were invasive carcinoma, and 56.7% were mixed. An MRI lesion correctly identified the histopathologically-defined cancer in 85.9% of DCIS cases, and to an even higher extent in invasive (97.0%) or mixed (98.1%) cases. DCIS often appears as non-mass clumped enhancement on MRI, with ductal or segmental distribution (7).

In a retrospective study with a median follow-up of five years of 1,019 women with family histories of breast cancer, the positive predictive value of MRI screening was evaluated. 37% of these patients had MRIs, resulting in detection of nine cancers, seven of which were detected by MRI only (8). The positive predictive value of MRI was 13% in those patients with the strongest family histories and about half that in those with less significant histories. These Investigators suggested that MRI should not be used as a general screen, but should only be reserved for those at highest risk.

Baltzer et al. identified criteria for false-positive findings in clinical practice with breast MRI (9). Breast MRI examinations of 132 patients with 120 malignant and 31 benign lesions from a consecutive 16-month time period that were classified as BI-RADS (Breast Imaging-Reporting and Data System) category 4-6 in the initial MRI report and that had histopathological verification were used. Lesions were categorized into mass or non-mass by two blinded observers and used BI-RADS to identify descriptor distribution differences between the benign and malignant subgroups. The ratio of mass to non-mass lesions differed significantly (p < 0.001) between benign and malignant findings. Seventeen mass and 14 non-mass lesions were false-positive, and 105 mass and 15 non-mass lesions were true-positive. It was possible to differentiate malignant and benign lesions on the basis of margin (smooth, irregular, or spiculated) and dynamic enhancement features among mass lesions. However, among non-mass lesions, only stippled enhancement had a significant difference between the subgroups. Thus, non-mass lesions were found to be the major cause of false-positive breast MRI findings; and BI-RADS descriptors were not sufficient for differentiating benign and malignant non-mass lesions.

Invasive lobular carcinoma (ILC) of the breast has a diffuse infiltrative growth pattern, presenting a diagnostic challenge; only up to 80% are visible at mammography. Moreover, both mammography and US tend to structurally underestimate the size of ILC. Mann reviewed outcomes in which ILC was initially detected with MR imaging (10). The size of an ILC as reported on MR imaging was found to correlate well with size at pathology. Additional tumor foci were detected by MR imaging, compared to mammography and US, in approximately one-third of patients, and these foci were confirmed histopathologically in 88% of cases. Thus, preoperative MR imaging of ILC directed patient management changes in almost 30% of cases. Mann concluded that when MR imaging findings were supported by second-look US or by MRI-guided biopsy, preoperative MR imaging reduced the rate of re-excisions after breast-conserving surgery from 27% to 9%, without increasing the rate of mastectomies and without extending total therapy time (10); further, that the early detection by MR imaging of contralateral carcinomas in ~ 7% of ILC patients suggested that preoperative MR imaging improved survival in these patients.

Another retrospective study examined the correlation between mammography, MRI and histopathology in 603 patients (11). Re-operation after lumpectomy occurred in 8.8% of patients due to positive margins, undetected by either form of imaging. Multi-centricity was identified by MRI alone in 7.7% of patients, whereas it detected contra-lateral cancer in 3.7% of patients. The sensitivity of MRI was 93% in detecting multi-centric disease and 88% for contra-lateral disease, far higher than for mammography: 46% and 19%, respectively. Similar results were obtained in other studies: MRI was much superior to mammography at finding DCIS (12-13).

Other studies have come to criticize the notion that MR imaging has real patient benefit. For example, Bloom and Morrow reviewed the controversial effects on patient outcomes (14). They noted that its use has not increased the likelihood of obtaining negative surgical margins, to decrease the rate of conversion from lumpectomy to mastectomy, or to decrease local recurrence. The rate of tumor identification by MR imaging is two-to-three-fold the incidence of local recurrence, resulting in needless mastectomies. Their explanation is that MR imaging alone for early detection of local recurrence does not consider the biology underlying local recurrence, since a short time to local recurrence equates to poor prognosis. Nevertheless, they conclude that in scenarios of evaluation of response to neoadjuvant therapy and detection of cancer presenting as axillary adenopathy, MR imaging enhances clinical management.

Similarly, a follow-up study (median, 4.6 years) of 756 women with early stage invasive breast carcinoma or DCIS, who at the time of initial diagnosis and evaluation received conventional mammography and then underwent breast-conserving treatment (15) included 28% who also received breast MRI evaluation. Comparing the outcomes for the women with vs. without pre-treatment breast MRIs, there were no differences in the 8-year rates of any local failure, local-only first failure, overall survival, cause-specific survival, freedom from distant metastases, or contra-lateral breast cancer.

In a recent review, Solin concluded that the routine use of pre-operative breast MR imaging was not indicated beyond conventional mammography and US correlation; this was based on the lack of consistent evidence for improving clinical outcomes or surgical procedures (16). A meta-analysis of studies of pre-operative breast MR imaging in the context of an established cancer, multifocal or multicentric disease was found on breast MRI in 16% of the patients: as noted before, substantially higher than the rate of local recurrence after breast conserving surgery plus definitive radiation treatment. Solin noted that the largest retrospective study of patients treated with breast conserving surgery plus radiation found no gain by adding a breast MRI to conventional breast imaging; however, no randomized clinical trial has been designed to evaluate long term clinical outcomes associated with adding a pre-operative breast MRI. Further, adding pre-operative breast MRI could possibly alter clinical management in harmful ways, including increased ipsilateral or contralateral prophylactic mastectomies, increased work-ups, and delay to definitive surgery.

Patients with Paget's disease of the nipple, usually associated with underlying breast cancer, have been studied with regard to the possible benefit of MR imaging for their optimal management. The numbers of studies, as well as the numbers of patients enrolled, are rather limited, some being only case reports. Nevertheless, the overall trend, described below, appears to consistently support a role for MRI in management of this disease.

Amano et al. reported a case study of a woman with skin color change of her right nipple for 11 months (17). No breast mass was palpable, and mammography failed to show any density or calcification. Nipple biopsy revealed Paget's disease with DCIS in the breast epithelium just beneath the nipple. MR imaging of the breast demonstrated diffuse segmental enhancement in two different quadrants. According to the pattern of enhancement, the lesions depicted by MR imaging were diagnosed as an extensively spreading type of DCIS. Following total mastectomy, histopathological examination demonstrated non-invasive ductal carcinoma with comedo-necrosis. The histological mapping demonstrated an extent of the lesions that corresponded accurately to the lesions defined by MR imaging. They concluded that MR imaging may be useful in selecting candidates for breast-conserving therapy out of those patients with mammary Paget's disease with no clinical evidence of an underlying breast carcinoma. In another case report, Capobianco et al. described a patient with a red lesion of the left nipple-areola complex (18). Breast physical examination, US and mammography were normal bilaterally; MR imaging correctly depicted Paget's disease of the nipple. Before surgery the patient underwent biopsy that showed Paget's disease associated with an underlying DCIS. The patient underwent left mastectomy and unilateral axillary lymph node dissection. Microscopy of the lesion confirmed the MRI diagnosis. They concluded that MR imaging was valuable

and accurate to diagnose Paget's disease of the breast without palpable mass, US and mammographic findings.

Echevvaria et al. analysed the ability of MR imaging to detect occult breast cancer in three patients with histologically-proven Paget's disease of the nipple-areolar complex (19). In all cases, differences in the morphological and dynamic features of healthy and pathological nipples were observed, as were enhancement foci in breast tissue; for two patients, these corresponded to DCIS. They concluded that detection and location of underlying neoplastic foci with MR imaging might be useful in selection of optimal treatment in these patients.

Frei et al. described retrospective MR imaging findings in patients with Paget's disease of the breast (20). Nine patients with biopsy-proven Paget's disease of the nipple underwent preoperative mammography and breast MR imaging, and all underwent subsequent surgery. Histopathology confirmed Paget's disease of the nipple in all patients and diagnosed associated DCIS in the retroareolar lactiferous ducts in eight of them. MR imaging showed abnormal nipple enhancement in the latter, with an ill-defined thickened nipple-areolar complex. DCIS elsewhere in the breast was diagnosed in four patients, corresponding to non-focal MR imaging enhancement.

Haddad et al. analyzed clinical, radiological, and histological data from six patients with Paget's disease (21). No patient presented a palpable mass or a suspicious anomaly on mammography. On MR imaging, the aureola-nipple plaque was morphologically abnormal in four cases, with suspicious enhancement in two DCIS cases. In two other cases, the aureola-nipple plaque was normal, and distant abnormal enhancement of the aureola-nipple plaque was noted in two cases. These Investigators concluded that the MR imaging aspect of the aureola-nipple plaque demonstrated little concordance with the histopathology, and that it could be useful in detecting distant lesions when there was neither a clinical sign nor a suspicious mammography.

Kim et al. retrospectively evaluated the significance of nipple enhancement of Paget's disease in contrast enhanced (CE) breast MR imaging (22). Ten patients with biopsy-proven Paget's disease and preoperative mammogram and US were followed, eight of whom underwent CE breast MR imaging prior to surgery. By MRI, morphology and enhancement of pathologically involved nipple were analyzed, comparing contralaterally, and the abnormal enhancing lesion in the breast parenchyma were included. Morphological changes of the nipple were detected in two patients by mammography and in six by US; changes were also revealed in seven patients and abnormal enhancement of involved nipple was observed in all eight. In seven patients, associated parenchymal enhancing lesions proved to be DCIS and in two, invasive ductal carcinoma. The remaining patient had no underlying breast parenchymal malignancy.

Morrogh et al. reported the largest Paget's disease study where patients were pre-operatively assessed by mammography and

MRI (23). Cancer was identified by histopathology in 94% of 34 patients; however, pre-operative imaging only detected 49% of these cancers. Following positive mammography, MRI findings did not influence patient management, whereas after negative mammography, MRI frequently detected otherwise occult disease. These Investigators concluded that negative pre-operative imaging was unreliable in excluding an underlying cancer in these patients, but since the increased sensitivity of MRI could detect occult disease, it could be considered for treatment planning in Paget's disease patients in the setting of negative mammography.

Patient eligibility for partial breast irradiation, as part of a breast-conserving strategy, was assessed by MRI for detecting cancers outside of the proposed radiation volume compared with mammography alone (24). Of 450 patients with non-metastatic, invasive breast cancer, 110 patients were deemed eligible for partial breast irradiation by criteria based on mammography, US, and initial pathology. Patients were randomized to receive either whole-breast or partial breast radiotherapy. MRI was used to identify secondary lesions within the same quadrant (multi-focal), in a different quadrant (multi-centric), or in the contra-lateral breast, any of which findings would have rendered the patient ineligible for partial breast radiotherapy. MRI correctly identified secondary lesions in 10% of patients, and its positive predictive value was 72.2%. These Investigators suggested that, to minimize local failures, MRI should therefore be considered to assess partial breast irradiation eligibility. A similar ability to detect secondary lesions by MR imaging resulting in ineligibility for accelerated partial breast irradiation has been reported by others (25-26).

Straver et al. attempted to establish a MR imaging-based interpretation model to facilitate the selection of breast-conserving surgery (BCS) after neoadjuvant chemotherapy (NAC; 27). Dynamic contrast-enhanced (DCE) MRI was performed in 208 patients, before and after NAC. Imaging results were found to correlate well with histopathology. Multivariate analysis was performed to analyze features affecting the potential of MRI to correctly indicate BCS, meaning residual tumor size <30 mm by histopathology. The accuracy of MRI to detect residual disease was found to be 76%; the positive and negative predictive values were 90% and 44%, respectively. In about one of six patients, MRI underestimated the tumor size by >20 mm, and in 13%, this would have lead to incorrect indication of BCS. These Investigators concluded that the optimal patient selection for BCS after NAC based on MRI should take into account (1) the tumor size at baseline (2) the reduction in tumor size, and (3) the subtype based on hormone-, and HER-2-status.

Pengel et al. assessed whether preoperative CE MR imaging of the breast influenced the rate of incomplete tumor excision (28). A cohort of 349 women with invasive breast cancer was used to compare patients eligible for BCS on the basis of conventional imaging and palpation only (N = 176) vs. those who had additional preoperative MR imaging (N = 173). By multivariate analysis, MR imaging detected a larger extent of breast cancer in 11% of women, leading to more extensive treatment, either mastectomy (8.7%) or wider excision (2.3%). Tumor excision was incomplete in 13.8% of the MR imaging group, but in 19.4% in the counterpart group (P = 0.17). Stratified to tumor type, incompletely excised infiltrating ductal carcinoma (IDC) was significantly associated with absence of pre-treatment MR imaging: 11/136 vs. 2/126 with MRI present (P = 0.02). Thus, preoperative MR imaging did not significantly affect the overall rate of incomplete tumor excision, but it yielded a significantly lower rate of incompletely excised IDC.

Inflammatory breast cancer (IBC) represents an extremely virulent albeit low-incidence subtype of breast cancer, for which improvements in management and outcomes are urgently needed. To identify typical MRI features of IBC in comparison with non-IBC locally advanced breast carcinoma, MRIs of 48 patients with IBC were compared with 52 closely-matched subjects with locally advanced disease (29). These parameters were observed more frequently with IBC: edema, thickening and pathologic enhancement of Cooper's ligaments, skin thickening, and "punched-out" signs: a focal increase of dermal or subcutaneous aspects followed by slow image enhancement of surrounding skin. Similar findings have been made in other studies of MRI and IBC (30-31).

The diagnostic effectiveness of computed tomography/ positron emission tomography (CT/PET), MRI, US, and mammography were compared in eighty IBC patients (32). Breast parenchymal lesions, skin abnormalities, regional nodal disease, and distant metastatic disease were considered in this comparison. Breast parenchymal lesions were found in 75% of patients scanned by mammography, in 95% of those scanned by US, in 96% of those scanned by PET/CT, and in 100% of those who had MRI analyses. Regional axillary nodal disease was found in 93% of patients by histopathologic or cytologic examination, in 93% of patients by US, in 88% by PET/CT, in 88% on MRI, and in only 45% by mammography. This result underscores the inadequacy of current mammographic guidelines for effective IBC imaging.

MRI has also been evaluated for distinguishing IBC from acute mastitis (AM; 33). No differences were apparent between the IBC and AM groups with regard to the morphology of masses, breast enlargement, diffuse skin thickening, abnormal nipple configuration, prominent vessels, or edema. Nevertheless, more masses with a greater average size were detected for IBC; and the main localization of AM was subareolar, whereas for IBC, it was central or dorsal.

Despite the positive evidence supporting the use of MRI in IBC diagnosis, there is unfortunately currently scant evidence that treatment decisions or outcomes are significantly impacted. One study examined 814 newly-diagnosed IBC patients over a five-year period to establish any correlation between pre-operative use of MRI and subsequent surgical treatment (34). Of these, 562 underwent breast conservation treatment, 151

chose mastectomy alone, and 101 chose mastectomy with reconstruction. Using multivariate analysis, it was determined that the factors associated with MRI use included multi-focality, younger age, tumor size, lobular histology, body mass index, and genetic testing. The use of MRI increased in practice over this five-year period, but without a significant impact on the type of surgery elected.

In summary, despite current high-profile use of MRI in evaluation of newly-diagnosed breast cancer patients, including DCIS, invasive carcinoma, and IBC, as well as in decisions of eligibility for breast-conserving treatment options, overall the results to date are far from satisfying in terms of clinical outcomes and improvements in treatment decisions (35-38).

The use of DCE-MRI employing gadolinium (Gd)-based contrast agents (CAs) is finding increasing applications in the detection and monitoring of breast cancer. DCE-MRI benefits from the current trend towards imaging at larger magnetic fields (3 T), which improve the signal-to-noise ratio of the images (39). However, CAs with even higher relaxivities are needed for patients who, for psychological or physical reasons, can only be scanned in open (low field) magnets (40). Semiquantitative DCE-MRI is the method of choice in breast imaging because of the long acquisition times required for a fully quantitative analysis. This limitation can be overcome by the use of CAs and new algorithms for image analysis, as was demonstrated by a computer simulation and analysis of 39 clinical breast cancers, which allowed the determination of volume transfer constant and extracellular volume fraction, two parameters required for the diagnostic accuracy of tumors (41).

While DCE-MRI is quite sensitive (>93%) for detecting breast carcinomas, its selectivity for discriminating malignant versus benign tumors is low. However, these two types of lesions can be differentiated on the basis of their washout patterns by kinetic analysis of contrast enhancement: the study of three known mammary tumor models imaged with Gd-diethylenetriamine penta-acetic acid (Gd-DTPA) showed that approximately 40% of the tumor volume lacks efficient washout (42). The determination of wash-in and wash-out parameters (WiP and WoP) by DCE-MRI was shown to be a potentially accurate predictor of a patient's response to hyperthermia and neoadjuvant chemotherapy in a study of 20 locally advanced breast cancer patients (43). The pharmacokinetic analysis of a Gd-DTPA-derived CA was used to determine the vascular leakiness of experimental tumors; vascular leakiness was shown to correlate well with the retention of cytotoxic drugs by the tumors, which could help in the optimization of therapeutic regimes (44).

MRI and Ovarian Cancer Management

Ovarian cancer is the sixth most common malignancy in women, accounting for ~3% of all female cancers, and it is the second most common and most lethal gynecological malignancy (45-46). Early stage disease is usually devoid of definitive

symptoms, although the "silent killer" characterization has recently been challenged (47-48); nevertheless, initial diagnosis is usually made at advanced tumor stages. Among risk factors, family history is the strongest; however, only ~10% of cases having a hereditary basis. Lifetime risk of ovarian cancer is up to 30% in individuals carrying mutations in BRCA1 and BRCA2 (49). Other risk factors include nulliparity, early menarche, and late menopause (50). Given the marked influence of tumor stage on prognosis in ovarian cancer, the need for effective early detection and distinct disease markers is widely appreciated. However, CA125, the benchmark serum-based assay for monitoring disease response and progression in ovarian cancer patients, is not useful in this regard due to inadequate sensitivity and specificity (51-52), and no other markers are currently widely accepted (53-54); further, no form of diagnostic imaging has emerged as useful for general screening purposes.

US is primarily used for characterization of adnexal (adnexa uteri) masses, and CT and PET are primarily used for initial staging and restaging of recurrent disease, whereas MRI can be used as a problem-solving tool for the characterization of complex ovarian masses, and also for staging of known ovarian carcinoma (55-60). MRI has proven value in definitively diagnosing common benign adnexal lesions. The major advantage of MRI in adnexal mass evaluation lies in its specificity; prospective analysis of women with a suspected adnexal mass who underwent both Doppler US and MRI revealed very high sensitivity for identifying malignant lesions by either modality, but the specificity of MRI was more than double that of US (61). Thus, those women who are best served by MRI in this setting are those with a low risk of malignancy and indeterminate lesions on US. A meta-analysis evaluating a second test for an indeterminate adnexal mass detected on gray scale US determined that MRI, with administration of IV CAs, provided the most reliable indicator of ovarian cancer when compared with CT, US, or MRI without administration of CA (62).

In a prospective analysis of ovarian cancer patients, CA-enhanced MRI showed sensitivity and specificity of 100% and 94%, respectively, in diagnosis of malignancy when evaluating an indeterminate mass detected by US (62). For epithelial ovarian tumors, the predominant type of ovarian cancer, MRI features are comparable to those seen with CT and US imaging: predominantly cystic lesions with solid components, the major criteria for a malignant diagnosis including a large solid component, with wall and septal thicknesses > 3 mm, nodularity, and necrosis (63). These major criteria are complemented by others for definitive diagnosis of a malignancy: involvement of pelvic organs or sidewall, peritoneal, mesenteric, or omental disease, ascites; and adenopathy. When the parameters for these criteria are pooled, high sensitivities and specificities for malignancy are achieved (62).

Borderline ovarian tumors (BTs) are an intermediate category of epithelial ovarian tumor, that histologically demonstrate

cellular proliferation and moderate nuclear atypia, but without stromal invasion (64). BT occur in all types of epithelial ovarian tumors, but are most common in serous and mucinous subtypes (65). Accurate preoperative characterization of ovarian tumors into benign, BT, and malignant lesions consequently influences surgical management. It has not yet been possible to distinguish between BTs and early malignant tumors. BT are rarely diagnosed preoperatively because they lack diagnostic imaging features that distinguish them from benign or early malignant epithelial tumors (64). On MRI, BT are predominantly cystic, and may feature numerous solid mural nodules or thick septa that enhance with Gd-CA administration (62).

Other studies have shown a high sensitivity of Gd CA-enhanced MRI for depicting small peritoneal tumors and carcinomatosis (66). Peritoneal tumors often enhance slowly, and complex upper abdominal peritoneal anatomy neighboring the liver, stomach, and pancreas render detection of small enhancing peritoneal tumors problematical. Recently, diffusion-weighted (DW) MRI has been investigated retrospectively in a complementary setting to MRI and found to improve characterization of peritoneal tumors (67). Interestingly, sheets of peritoneal tumor could best be seen on the delayed Gd CA-enhanced MR images because of their marked enhancement.

Targeted MRI Contrast Agents (CAs)

Advances in the application of MRI in cancer screening, staging, and treatment have been hampered by the poor tumor-to-background ratio that MRI provides. In order to improve this ratio, the development of CAs with enhanced sensitivity (three to four orders of magnitude) and targeting is desired. Targeted MRI-CAs offer another dimension of molecular specificity to the abundant anatomical and functional information that MRI already provides. Targeted CAs are synthesized by the conjugation of a reporter group (such as Gd-chelates and iron-oxide particles) to a high-affinity ligand able to recognize and bind to specific receptors or biomarkers at the cellular membrane. Target binding provides the pharmacodynamic effect of increasing the relaxivity of the contrast agent, and therefore the MR signal. Due to the low sensitivity of MRI and the low concentration of most cellular targets, the development of amplification strategies based on multiple reporter groups bound to a single targeting moiety to amplify the signal is being exploited, since it circumvents both limitations. Gd-based CAs, superparamagnetic iron oxides (SPIOs) and ultrasmall SPIOs (USPIOs), which also act as MRI-CAs, as well as biodegradable natural nanoparticles (lipoproteins, viruses, or ferritin), which are loaded with Gd-ions, SPIOs, gold nanoparticles, etc., can be rerouted from their natural targets through the attachment of directing molecules (68-72). Some typical biomarkers of breast and ovarian cancer cells are the folate receptors (FR), CD20 and CD44, which are overexpressed on both those types cells (73, 74). Consequently, current research efforts towards clinical applications of MRI for the detection of breast and ovarian cancers are focused on the synthesis and evaluation of CAs targeting those biomarkers. The following paragraphs summarize some recent efforts in that direction.

While signal-to-background ratios improve in higher-magnetic field scanners, there are construction and cost issues that currently limit the magnetic field of clinical scanners to 1.5 T. Larger magnetic fields are available in instruments with small animal probes, or in experimental scanners. Concerns regarding possible adverse physiological effects of large magnetic fields on humans may eventually prevent the development of clinical scanners with larger fields. Consequently, it is essential to increase the signal-to-noise ration by other means. In a study by Neumaier et al., tumor bearing mice were injected with human natural killer T cells labeled with an USPIO. A 35% increase in transverse relaxation time was achieved in in vivo MR images of human breast cancer cells at 1.5 T. The results obtained with this targeted CA were comparable with those previously achieved only in 3.5 – 7 T magnets (75).

Efficient targeting of the tumor cells was achieved using a CA composed of USPIOs coated with polyethylene glycol (PEG) conjugated to octeotride (OCT). In a study involving in vivo MRI (3 T) assessment of 24 mice bearing implanted human MCF-7 breast adenocarcinomas, the USPIO-PEG-OCT CA was shown to bind specifically to MCF-7 cells, producing a significant decrease of the transverse relaxation time compared to a control group (76). Trastuzumab (Herceptin) is a monoclonal antibody used in the targeted therapy of HER-2(+) breast cancers. Dextran-modified SPIOs conjugated to Herceptin were used in a preclinical study of HER-2(+) breast cancer-bearing mice by T2-weighted MRI (3T), achieving a 45% signal intensity drop within the tumor sites (77). Both Oct and Herceptin are promising targeting goups to improve the sensitivity of CAs.

Ovarian tumors implanted in rats were imaged following injection of two FR-targeted -- P866 (Gd-chelate) and P1048 (SPIO) -- and two non-targeted -- P1001 (Gd-chelate) and P904 (SPIO) -- CAs. Changes in longitudinal and transverse relaxation rates (Δr1 and Δr2), which were proportional to the CA concentration in the tumors, were compared between tumors injected with FR-targeted and nontargeted agents. The tumors showed uptake of P866 and P1048, which decreased with competing free folate. The Δr1 values were higher at 1 h following injection of P866 than following injection of P1001, indicating a higher amount of CA retained in the tumor following injection of the targeted CA. There was a similar, but statistically not significant, trend in Δr2 values at 48 h following injection of P1048 compared to injection of P904. The experiments suggested a specific accumulation of P866 in an FR-positive ovarian tumor model, demonstrating the feasibility of the method to improve diagnosis and treatment of FR-positive tumors (78). Another study by Meier et al. assessed the ability of a FR-targeted USPIO, P1133, compared to a non-targeted USPIO, P904, to provide FR-specific enhancement

of FR-positive breast cancers in T2-weighted MR images. Of twenty one athymic rats, six were implanted with FR-positive MDA-MB-231 breast cancers and were injected with P133, nine were implanted with FR-negative A549 lung cancers and were also injected with P1133, and six were implanted with FR-positive MDA-MB-231 breast cancers and were injected with P904. Only the MDA-MB-231 showed specific retention of USPIOs and significant effect on the signal-to-noise ratio. These effects were inhibited by free FA (79). Visible by MRI changes to ovarian tumors borne by mice have also been achieved by targeting the tumors with a supramolecular avidin-biotin-(Gd-DTPA-dendrimer) assembly (80).

In summary, the value of MRI and DCE-MRI has already been demonstrated in the area of breast cancer detection, while further advances are expected in the future. In contrast, and despite considerable efforts, a clear cut case has not been yet made for the earlier detection of ovarian cancer by either MRI or CA-enhanced MRI. However, several preclinical research results have provided an optimistic outlook for the future. It is in the latter context that we expect that molecularly-targeted CAs might allow in the near future earlier intervention following a rising CA125.

Abbreviations

Acute mastitis - AM, Borderline ovarian tumor - BT, Breast cancer 1, early onset gene - BRCA1, Breast cancer 2, early onset gene - BRCA2, Breast-conserving surgery - BCS, Breast Imaging-Reporting and Data System - BI-RADS, Computed tomography - CT, Contrast agents - CA, Contrast enhanced - CE, Diethylenetriamine penta-acetic acid - DTPA, Diffusion-weighted - DW, Dynamic contrast-enhanced MRI - DCE-MRI, Ductal carcinoma *in situ* - DCIS, Folate receptor - FR, Infiltrating ductal carcinoma - IDC, Inflammatory breast cancer - IBC, Invasive lobular carcinoma - ILC, Magnetic Resonance Imaging - MRI, Magnetic Resonance Imaging Contrast Agent - MRI-CA, National Comprehensive Cancer Network - NCCN, Neoadjuvant chemotherapy - NAC, Octeotride - OCT, Polyethylene glycol - PEG, Positron emission tomography - PET, Superparamagnetic iron oxide - SPIO, Ultrasmall superparamagnetic iron oxide - USPIO, Ultrasound - US, Wash-in parameter - WiP, Wash-out parameter - WoP

Resumen

La representación de resonancia magnética (MRI) ocupa un lugar creciente en el diagnóstico clínico de varios cánceres, incluso cánceres del seno. A pesar del nivel alto de la realización de la mamografía, se ha hecho aparente que la MRI puede desempeñar al menos un papel complementario en la representación y diagnóstico de cánceres del seno primarios, incluso la carcinoma ductal *en situ*, la etapa más temprana del cáncer del seno que tiene que ver con un riesgo aumentado del cáncer del seno invasivo. Este también puede ser dicho del cáncer del seno inflamatorio, de frecuencia baja, pero con impacto alto en tasas de mortalidad de cáncer del seno totales, y para que la mamografía no es ideal debido a la naturaleza típicamente difundida de esta enfermedad. La mayor parte del valor de la MRI de seno es dependiente de su sensibilidad alta, que resulta del uso del realce de agente de contraste en el descubrimiento de cáncer del seno. El interés también ha aumentado en la aplicación de la MRI ponderada de difusión para la evaluación temprana de la respuesta de tratamiento de esta enfermedad. En cuanto a cánceres ginecológicos, ováricos y otros, la MRI ha demostrado ya el valor en la evaluación de pacientes con masas ováricas, leiomyoma uterino, endometrioma, y cáncer cervical. Los rasgos en la MRI que sugieren tumores ováricos malignos son variados, y atraviesan componentes irregulares o sólidos a una masa cistica, reptaciones prominentes, evidencia de extensión peritoneal, hematógeno, o linfática, o invasión local. La mayoría de la malignidad ovárica es diagnosticada en etapas avanzadas, incurables, donde el exploratorio laparotómico proporciona la oportunidad de desabultamiento máximo. Aunque un papel para la MRI tenga que ser establecido aún en este ajuste inicial o en la organización, algunos estudios han mostrado que la sensitividad alta puede ser conseguida con MRI realzado por agente de contraste para la detección de la enfermedad recurrente, incluso la demostración de la diseminación intraabdominal macroscópica y el sello omental "pastel". Los esfuerzos en años recientes han sido enfocados en el diseño de agentes de contraste de MRI (CA de MRI), que apuntan a biomarcadores, o aprovechan la fisiología diferente de células cancerosas. CA de MRI basados en complejos de gadolinio, ferrumóxidos, y otras nanopartículas metálicas han sido investigadas. Esta revisión se concentrará en el progreso reciente en la aplicación de MRI a la representación de cánceres de seno y ováricos, y presentará un papel posible para agentes de contraste molecularmente apuntados en el enriquecimiento del contexto para el diagnóstico a base de MRI.

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