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Original contribution

Relationship between morphological features and kinetic patterns of enhancement of the dynamic breast magnetic resonance imaging and tumor expression of metalloproteases and their inhibitors in invasive breast cancer

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ABSTRACT

Aim: Matrix metalloproteases (MMPs) expression and their inhibitors (TIMPs) play an important role in tumor physiopathology, so we investigated the relationship between the magnetic resonance (MR) and MMPs/TIMPs expression by breast carcinomas.
Materials and methods: MRI parameters of 64 breast carcinomas were investigated. An immunohistochemical study was also performed in these cases using tissue microarrays and specific antibodies against MMP-1, MMP-2, MMP-7, MMP-9, MMP-11, MMP-13, MMP-14, TIMP-1, TIMP-2 and TIMP-3.
Results: Tumors with spiculated margins had a high global (score) values of MMP-1 or MMP-7, and high expression of TIMP-3 by tumor cells. Heterogeneous tumors had a higher score values of MMP-1, MMP-13, TIMP-2 or TIMP-3, and frequent expression of TIMP-3 by tumor cells. Tumors showing fast enhancement, had higher score values of MMP-1 or MMP-11. Associations between washout curve (type III) and MMP-1, MMP-11, MMP-13 and TIMP-1 expression by tumor cells, were found.
Conclusions: MRI features may predict in some grade the expressions of MMPs/TIMPs in breast tumors, which might to contribute to a better biological characterization of breast cancer.

1. Introduction

Magnetic resonance (MR) is increasingly used in the workup of breast cancer patients and has become an indispensable tool in the diagnosis. It plays an important role in the evaluation of the extent of breast cancer by revealing multifocal tumor growth in patients who are candidates for conservative breast surgery, directly influencing the therapeutic management [1,2]. Recently, MRI appears to have an important value in estimating other aspects of interest in breast cancer, such as the assessment of axillary lymph node metastasis, or the prediction of the clinicopathological response to primary chemotherapy, providing that it could detect any residual disease present [3].

MR permits us to analyze the morphologic characteristics of the lesions with high spatial resolution, such as the margin morphology (smooth, irregular or spiculated) or the internal architecture of the tumors (represented as internal mass enhancement: homogeneous, heterogeneous or rim enhancement) [1,4]. Also it permits us to obtain dynamic data derived from the kinetic patterns of lesion enhancement after the administration of contrast material [5], which include the behavior of the signal intensity in the early phase after the administration of contrast material, and the late postcontrast period. Likewise, this time course may be visualized in 2D and 3D dynamic MR series. These time–signal intensity curves allow us to determine whether the signal intensity continues to increase after the initial upstroke, cuts off and reaches a plateau, or if it just washes out. It has been demonstrated that this latter curve type is a strong indicator of malignancy, being independent of other criteria [6]. These both morphologic and kinetic patterns that display variability among tumors may reflect the different biological behavior of breast carcinomas. In fact, there are studies indicating that dynamic

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contrast-enhanced MR helps us to predict prognosis from patients [7], as well as prognostic factors and biological activity of breast cancer by revealing of the primary tumors, such as angiogenesis [8,9], degree of fibrosis [8], histological grade [10,11], negative expression of estrogen receptor and progesterone receptor [11], vascular endothelial growth factor (VEGF) expression [8], HER-2 overexpression [12], microvessel density, vascular invasion or peritumoral inflammation [9]. Also MR detects changes in microvascular permeability in xenograft tumors after treatment with a matrix metalloprotease (MMP) inhibitor [13].

The human MMP family currently consists of 28 members of homologous zinc-dependent endopeptidases that can be divided into eight structural classes or, on the basis of their substrate specificity and primary structure, into the more familiar subgroups of collagenases (MMP-1, MMP-8, and MMP-13), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3, MMP-10, and MMP-11), membrane-associated MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-23, MMP-24, and MMP-25), and other novel MMPs [14,15].

MMPs play an essential role in the degradation of the stromal connective tissue and basement membrane components, which are key elements in tumor invasion and metastasis. MMPs are able to impact *in vivo* on tumor cell behavior as a consequence of their capacity to cleave growth factors, cell surface receptors, cell adhesion molecules, and cytokines [16,17]. Furthermore, by cleaving proapoptotic factors, MMPs produce a more aggressive phenotype *via* generation of apoptotic resistant cells [18]. MMPs also regulate cancer-related angiogenesis [19,20]. The activity of MMPs is specifically inhibited by the so-called tissue inhibitors of metalloproteases (TIMPs). Four different TIMPs are known to exist: TIMP-1, TIMP-2, TIMP-3, and TIMP-4.

Considering the importance of MMPs/TIMPs expression in tumor physiopathology, the objectives of this study were to investigate the relationship between the MR features of breast cancer and MMPs/TIMPs expression by breast carcinomas, which might to contribute to a better biological characterization of breast cancer across to the diagnostic imaging.

2. Materials and methods

2.1. Patient selection and characteristics

This study compromised 64 women consecutively diagnosed of early invasive breast cancer (without distant metastases at time of initial diagnoses) and treated between 1999 and 2006. Initially, the lesions were detected by physical examination, mammography or ultrasonography. All of the women did not receive any type of neoadjuvant therapy. The features of our patients evaluated in this study are listed in Table 1.

The histological grade was assessed according to criteria reported by the Nottingham Modification of Bloom and Richardson Score (SBR).

Women were treated according to European international guidelines. The study adhered to national regulations and was approved by the Research Ethics Committee of our institution.

2.2. MR imaging

As described previously by Fernández-Guinea et al. [9], MR was performed at 1,5 Tesla (Echospeed Signa; General Electric Medicale Systems, Milwaukee, WI, USA). After the informed consent was obtained, patients were placed in the prone position and examined using standard dedicated bilateral breast coils. The imaging protocol consisted of an initial scout view that provided axial, coronal, and sagittal images of both breast. The subsequent axial dynamic series were then positioned to cover the whole parenchyma.

Table 1
Patients and tumor characteristics.

Characteristics	N = 64
Age (years)	
Average	57
Interval	30–83
Menopausal status	
Premenopausal	26
Postmenopause	38
Tumor size	
T1	40
T2	20
T3/4	4
Nodal status	
N0	33
N+	30
Unknown	1
Histological type	
Ductal	51
Lobular	8
Mucinous	2
Other	3
Histological grade (SBR)	
I	22
II	25
III	17
Estrogen receptors	
Negative	13
Positive	51
Progesterone receptors	
Negative	19
Positive	45
Her-2	
Negative	32
Positive	24
Unknown	8

Before administration of contrast material, T1-weighted frames were acquired in the axial plane (FSPGR — fast spoiled gradient echo 3D; FA — flip angle, 10°; TR, 9,9 milliseconds; TE, 4,2 milliseconds; NEX, 1; 2–3 mm slice thickness with no gap; 512 × 192 matrix; in-plane resolution, 0,6 × 1,8; frequency was in the anteroposterior direction). Acquisition of dynamic imaging started 10s after the intravenous injection of 0,2/kg of gadopentetate dimeglumine (Gd-DTPA) (Magnevist; Schering, Madrid, Spain), followed by a 20 ml saline solution flush, at an injection rate of 2 ml/s, following by six series, which lasted 80 s each for a total imaging time of slightly over nine minutes.

2.3. Image analysis

All images were evaluated with the Functool algorithm on the Advantage Windows Workstation (General Electric Medical Systems).

After the dynamic series, image subtraction was performed to suppress the fat signal, and enhancing lesions were identified on the subtracted images. To verify the presence of a contrast-enhancing lesion and to exclude subtraction artifacts, we also re-identified the lesions on the non-subtracted images.

For each suspected lesion included in the dynamic slices, the following morphologic features were recorded: site, size, margins, and type of enhancement. To evaluate kinetics, a small region of interest (ROI) is placed selectively over the most intensely enhancing area of the lesion. The ROI size was always greater than three pixels, and without upper limit. The ROI was placed in the rim enhancement during the dynamic study, when the tumors showed this finding.