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Analysis of kinetic curve and model-based perfusion parameters on dynamic contrast enhanced MRI in breast cancer patients: Correlations with dominant stroma type

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ABSTRACT

Objective: Our purpose was to evaluate imaging findings of breast cancers according to the dominant stroma type by using kinetic curve analysis and model-based perfusion parameters from dynamic contrast-enhanced magnetic resonance imaging.
Methods: From March 2011 to September 2011, 64 cancers in 64 patients were included for data analysis. Kinetic curve analysis and model based perfusion parameters (Ktrans, Kep and Ve) were obtained using dynamic contrast-enhanced magnetic resonance imaging and post-processing software. Imaging characteristics were analyzed according to the tumor-stroma ratio and dominant stroma type.
Results: Ve values were significantly lower in tumors with more than 50% cellularity (0.44 vs. 0.29, $p = 0.008$). Histologic grade, estrogen receptor status and subtype of cancer (triple negative versus non-triple negative) were significantly different ($p = 0.009$, $p = 0.019$ and $p = 0.03$, respectively).
Median Kep values were different between collagen dominant, fibroblast dominant and lymphocyte dominant groups. By post hoc comparisons, mean Kep values were significantly higher in lymphocyte dominant group than collagen dominant group ($p = 0.003$). Ktrans and Ve values were not significantly different according to dominant stroma type ($p = 0.351$ and $p = 0.257$, respectively). In multivariate regression analysis, nuclear grade ($p = 0.021$) and dominant stroma type (collagen dominant, $p = 0.017$) were independently correlated with Kep values. In terms of the dominant stroma type, the collagen dominant type showed a decrease of 0.247 in Kep values, compared with the fibroblast-dominant type ($p = 0.017$).
Conclusions: Ve values were significantly lower in tumors with high tumor-stroma ratio. Kep values were significantly lower in breast cancers with dominant collagen type and higher in cancers with high nuclear grade.

1. Introduction

Tumor cells are surrounded by the tumor microenvironment. Interaction between tumor cells and microenvironment is important for the initiation and progression of cancer. During the proliferation of malignant cells, there are a lot of changes in the tumor stroma, including increased angiogenesis, immune cell infiltration, remodeling of extracellular matrix and changes in pH and oxygen tension [1–4]. Fibroblasts are most frequent components in connective tissues and secretes extracellular matrix. Cancer-associated fibroblasts are activated fibroblasts in cancer stroma and promote tumor initiation, progression, invasion and metastasis in breast cancer [5–10]. The atypical fibroblasts or leukocyte infiltration in the tumor stroma were significant prognostic factors [11,12]. Previous study reported that the dominant stroma type of breast cancers was significant prognostic factor of disease free survival and the collagen dominant type showed the worst prognosis [13]. Lymphocyte infiltration in triple negative breast cancer has been associated with responsiveness to chemotherapy and better overall survival [14–16].

Dynamic contrast-enhanced magnetic resonance imaging could evaluate vascular characteristics of breast cancers because of increase blood flow and vascular permeability of tumor vessels. Three perfusion parameters are usually used for pharmacokinetic modeling in breast cancer imaging; forward volume transfer constant (Ktrans, expressed as min^{-1}), reverse volume transfer

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constant (Kep, expressed as min^{-1}) and extravascular extracellular space volume per unit volume of tissue (Ve) [17,18]. Perfusion parameters from dynamic contrast-enhanced magnetic resonance imaging were useful for the differentiation of benign and malignant breast tumors, and they were associated with poor histologic prognostic factors [19–22].

Extravascular extracellular space volume (Ve) could be different according to the dominant stroma type because tumor cellularity is different between collagen, fibroblast, and lymphocyte dominant types. Also, the degree of angiogenesis could be different according to the dominant stroma type. Our hypothesis was that collagen dominant type which is known to be associated with worst prognosis would have more increased angiogenesis compared to other types and would show initial fast and delayed washout kinetic curve pattern and higher perfusion parameters. Until now, there are few reports about the imaging findings of breast cancers according to the intra-tumoral dominant stroma type. As far as we know, only one study reported that ADC values of collagen dominant type were significantly lower than fibroblast or lymphocyte dominant types of estrogen receptor-positive breast cancers on diffusion weighted imaging [23]. Therefore, our purpose was to evaluate imaging characteristics of breast cancers according to the dominant stroma type by using kinetic curve analysis and model-based perfusion parameters from dynamic contrast-enhanced magnetic resonance imaging.

2. Materials and methods

2.1. Patients

This retrospective study was approved by our institutional review board with waiver of any need for informed consent. From March 2011 to September 2011, 194 consecutive patients with breast cancer underwent dynamic contrast-enhanced magnetic resonance imaging in our hospital.

Among these patients, 124 patients were excluded due to past history or planning of future neoadjuvant chemotherapy (n = 77), small size below than 1 cm (n = 17), non-mass like ductal enhancement pattern (n = 7), tumor excision or vacuum-assisted breast biopsy (n = 6), and impossibility of pathologic confirmation (n = 1), absence of available MR perfusion data (n = 7) and MR image not containing aorta (n = 9). During pharmacokinetic modeling analysis, we also excluded 6 patients who had cancers showing non-physiologic values of perfusion parameters (Ve > 1). Finally, 64 cancers in 64 patients were included for data analysis.

The mean patient age was 48 years (range, 30–67 years). Of 64 cancers, 2 lesions were papillary carcinomas, 1 was invasive lobular carcinoma and the remaining 61 were invasive ductal carcinomas of not otherwise specified type.

2.2. MRI techniques

All MR examinations were performed using 1.5T system (Signa HDxt; GE Healthcare, Milwaukee, WI) with a dedicated breast coil (8-channel HD breast array, GE Healthcare, Milwaukee, WI).

For the baseline T1 calculation, pre-contrast transverse 3D gradient-echo images were obtained using flip angle of 3° and 12° and the following parameters: TR/TE = 3.62/1.78 ms, FOV = 280 mm, matrix 200 × 200, number of slices = 40, slice thickness = 2 mm (interpolated), no gap, receiver bandwidth = 50 kHz. Dynamic contrast-enhanced magnetic resonance images were obtained using a non-fat-suppressed 3D fast spoiled gradient-echo (SPGR) sequence with parallel imaging acceleration through the entire breast using flip angle of 20° and same parameters with pre-contrast image. In total, 42 phases of images with a temporal resolution of 11 seconds were obtained before, during and after contrast injection.

Gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) was injected into an antecubital vein using an automated injector at a dose of 0.1 mmol/kg of body weight and at a rate of 3 mL/s, followed by a 20-mL saline flush for all patients.

2.3. Image analysis

For the kinetic curve analysis, we used the FuncTool Software (GE Healthcare, Milwaukee, WI). A region of interest was placed on the fastest-enhancing portion of the lesion or the most suspicious washout curve pattern in the lesion. The initial enhancement pattern was classified as slow (percentage contrast enhancement ratio within 2 minutes after contrast injection < 300%), medium (300%–500%), and rapid (>500%). The kinetic curve types were categorized into 3 types (persistent, plateau, or washout) on the images obtained during the last 16 consecutive phases after 2 minutes or after the curve started to change. A signal decrease of more than 10% is defined as a washout. A signal increase by more than 10% is defined as persistent. If a pixel value does not change in either direction by more than 10%, the enhancement pattern is classified as a plateau. From the kinetic curve, we obtained initial rate of enhancement which was calculated as follows: [(signal intensity at 2 min) − (signal intensity before contrast injection)]/2 min.

For the acquisition of perfusion parameters, post-processing of the high temporal resolution images was done using VizPack software (GE Healthcare, Milwaukee, WI). The arterial input function was measured in the aortic arch or in the highest level of scanned aorta, if the aortic arch is not scanned. Several regions of interest for arterial input function were positioned in the center of aortic lumen and a region of interest showing the highest maximal peak enhancement and fastest peak arrival time was selected as a single representative arterial input function. For the measurement of perfusion parameters of the tumor, region of interest was drawn manually around the tumor margins on three consecutive axial sections including the center of tumor mass. Care was taken to exclude adjacent soft tissues and blood vessels. The regions of interest of the tumor did not include central, poorly enhanced, low-attenuated areas, which were considered to be areas of necrosis. The mean value of the parameters within the regions of interest was automatically calculated and displayed and we took the highest mean value. All MR images were reviewed by two radiologists of 6 and 12 years of experience in interpreting breast imaging in consensus. The enhancement kinetics from each pixel was measured throughout the scan time and fitted with two compartment model by Tofts et al. [17,18].

2.4. Histological evaluation

Surgical specimens from the areas of the macroscopic tumor were serially sliced at 5-mm intervals, prepared as paraffin-embedded sections, and stained with hematoxylin–eosin. A pathologist with 17 years of experience reviewed the tumor-stroma ratio and predominant stromal component. The tumor-stroma ratio was scored to the nearest 10 percentage points based on methods described by Mesker et al. [24]. Three stromal components, the collagen, fibroblasts, and lymphocytes were also evaluated [13]. Stroma was described as collagen dominant when composed of broad bands of eosinophilic hyalinized collagen. Stroma was classified as fibroblast dominant when it consisted of randomly oriented immature collagen in a myxoid background or desmoplasia. Stroma that was predominantly composed of lymphocytes was considered as lymphocyte dominant.

The specimens were evaluated according to the following histopathologic features: histological type of carcinoma; Black's nuclear grade (NG, 1 — poorly differentiated, 2 — moderately differentiated, and 3 — well differentiated), modified Bloom–Richardson's histological grade (HG, 1 — well differentiated, 2 — moderately differentiated, and 3 — poorly