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Positive enhancement integral values in dynamic contrast enhanced magnetic resonance imaging of breast carcinoma: Ductal carcinoma in situ vs. invasive ductal carcinoma

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ABSTRACT

Objectives: The aim of this study was to contribute to the standardization of the numeric positive enhancement integral (PEI) values in breast parenchyma, ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) and to evaluate the significance of the difference in PEI values between IDC and parenchyma, DCIS and parenchyma and IDC and DCIS.
Materials and Methods: In the prospective trial, we analyzed the dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of 60 consecutive patients with histologically confirmed unilateral DCIS ($n = 30$) and IDC ($n = 30$) and defined the PEI values (range; mean ± SD) for the lesions and the breast parenchyma. Tumor-to-non-tumor (T/NT) ratios were calculated for DCIS and IDC and compared. PEI color maps (PEICM) were created. The differences in PEI values between IDC and parenchyma and between DCIS and parenchyma were tested according to *t*-test. Analysis of variance (ANOVA) was used to test the differences between the mean PEI values of parenchyma, DCIS and IDC.
Results: IDC showed highly statistically different PEI numeric values compared to breast parenchyma (748.7 ± 32.2 vs. 74.6 ± 17.0; $p < 0.0001$). The same applied to the differences in the group of patients with DCIS (428.0 ± 25.0 vs. 66.0 ± 10.6; $p < 0.0001$). The difference between IDC, DCIS and parenchyma were also considered highly statistically significant ($p < 0.0001$) and so were the T/NT ratios for IDC and DCIS (10.1 ± 2.4 vs. 6.6 ± 1.4; $p < 0.0001$).
Conclusions: PEI numeric values may contribute to differentiation between invasive and in situ breast carcinoma.

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1. Introduction

Positive enhancement integral (PEI) is the semiquantitative parameter, which represents the summation of the total signal above the baseline [1,2]. PEI, as the endpoint in tissue perfusion evaluation with different imaging modalities (CT and MRI), displays the area under the time-intensity curve on a pixel-by-pixel basis and has the role in quantitative evaluation and characterization of tissue perfusion [3]. PEI represents the integral of the area under the enhancement curve after the injection of contrast agent for the time-signal intensity (SI) graph acquired for the time (t) [4]:

$$\mathrm{PEI} = \sum_{0}^{t} x\,\mathrm{SI}_t$$

Apart from the range of PEI values for the selected region of interest (ROI) or the mean value ± SD, the parametric maps – PEI color maps (PEICM) can be calculated on a pixel-by-pixel basis from the acquired data, suitable for acquisition techniques with high temporal resolution [5].

In the clinical setting, PEI values have been interpreted as the tissue perfusion parameter, providing useful quantitative

Abbreviations: PEI, positive enhancement integral; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging.

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information, increasing the diagnostic value of extracellular gadolinium contrast agent in different physiologic tissues [6,7], enabling differentiation between benign and malignant tumors at 1.5 T and 3 T [2,8,9] and have been used in post treatment residual breast tumor evaluation [4].

Ductal carcinoma in situ (DCIS), the highly heterogeneous disease based on pathologic, clinical and radiological criteria, is defined as the clonal proliferation of malignant epithelial cells, which did not breach the myopethelial layer of ductolobular system [10]. DCIS is classified according to different criteria: architectural pattern (solid, cribriform, papillary and micro-papillary), tumor grade (low, intermediate and high) and the presence or absence of comedo histology [11]. DCE-MRI is used to characterize microvasculature – structure and function [12]. The tumor detection is related to angiogenesis, increased vascularity and permeability [13]. Although there are two distinct patterns of DCIS vascularization development: periductal and stromal, no significant association was found between the extent of DCIS vascularization and the histologic type [13,14]. Disruption of myopethelial cells is related to both – angiogenesis, microcirculatory environment and tumor invasion [13]. As the lesion progresses from in situ to invasive, the lesion perfusion rates become higher. The sensitivity of DCE-MRI in DCIS detection increases with higher nuclear grade [10,15]. DCIS enhancement rates on DCE-MRI remain below the typical enhancement thresholds of invasive cancers, leading to the conclusion that the criteria related to enhancement kinetics in breast carcinoma might not be useful in the diagnosis of DCIS [16].

Taking into consideration the above-mentioned facts concerning the vascularization of DCIS, enhancement threshold and insight into tissue and tumor perfusion with PEI, the purpose of this study was:

a) To contribute to the standardization of the PEI values in breast parenchyma, DCIS and invasive ductal carcinoma (IDC) and
b) To evaluate the significance of the difference in PEI values between IDC and parenchyma, DCIS and parenchyma and IDC and DCIS.

2. Materials and methods

The inclusion criteria included the histologic confirmation of either DCIS or IDC of the mammographically categorized BI-RADS 4 or 5 unilaterally present lesions [17]. The exclusion criterion was the presence of contralateral breast lesion(s). Sixty female patients were included in this prospective trial – 30 consecutive patients with histologically confirmed diagnosis of DCIS (48.2 ± 6.7 yr) and 30 consecutive patients with histologically confirmed diagnosis of IDC (54.8 ± 8.6 yr). The study was conducted from June 2010 until December 2012, following the decision of the Institution Review Board (IRB). Written informed consent was obtained from all patients. The patients ($n = 60$) were initially diagnosed with full-field digital mammography (FFDM). All patients were assigned BI-RADS category either 4 or 5 and were additionally examined with breast ultrasound (US) and DCE-MRI. The suspicious lesions were biopsied. Stereotactic-guided vacuum assisted biopsy or biopsy under palpation was performed 14 days before DCE-MRI exam. The nature of the lesions was histologically confirmed. The patients were examined with DCE-MRI prior to multidisciplinary team decision concerning the surgical intervention, as the preoperative DCE-MRI distinguishes the risk of invasive breast cancer and patients at low risk [18].

All patients with histologically verified lesions as DCIS ($n = 30$) and IDC ($n = 30$) were examined with DCE-MRI in the prone position. Breast MRI was performed with the 1.5 T MRI unit (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) with dedicated bilateral breast specific coil. The diagnostic protocol was used for the axial-plane images (slice thickness 2 mm): T2W TIRM (TE/TR 60/7690, inversion time 180 ms, flip angle 150, field of view 340 × 340, image matrix 320 × 256); T2W TSE (TE/TR 70/5900, flip angle 180, field of view 340 × 340, image matrix 384 × 319); T1W TSE (TE/TR 12/910, flip angle 90, field of view 340 × 340, image matrix 320 × 234); T1W FLASH 3D (TE/TR 4.8/9.1, flip angle 25, field of view 340 × 340, image matrix 576 × 564) one precontrast and five postcontrast series acquired every 1 min 23 s, after the bolus injection of 0.1 mmol/kg of body weight of gadopentetic acid Gd-DTPA (Magnevist, Bayer Schering Pharma, Berlin, Germany) with the automatic injector (Mississippi, Ulrich Medical, Ulm, Germany) at the rate of 2 mL/s, with the flush of 20 mL saline.

DCE-MRI series of images used for morphologic and kinetic analysis: pre- and postcontrast images, subtracted series, maximum intensity projection, multiplanar reconstruction, semi-quantitative analysis of the contrast medium kinetics with the creation of time-intensity curves (TIC) were also generated and analyzed on the standard workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany) using the image processing software Syngo (Syngo, Siemens Medical Solutions, Erlangen, Germany). PEICM were created (pixel-by-pixel), with the processing software Syngo and were further analyzed with the image processing software OsiriX (OsiriX, Pixmeo, Geneva, Switzerland). The region of interest (ROI) in the lesion was selected on the PEICM as the most enhancing part of the lesion. The second ROI in the breast parenchyma was automatically selected on the same coordinates in the parenchyma of the contralateral breast. The surface of the selected circle ROIs included 10 pixels, as ROIs larger than 4 pixels are recommended in breast DCE-MRI [19].

The PEI values for the selected ROIs were described as the mean value ± SD and as the range from minimal to maximal value for lesion and parenchyma. The mean was calculated for the PEI values for each group of patients. Tumor-to-non-tumor (T/NT) ratio was calculated according to the following model: $T/NT = (TU_{PEI[mean]}/NT_{PEI[mean]})$. The differences in PEI values between IDC and parenchyma and between DCIS and parenchyma were tested according to *t*-test [20]. Analysis of variance (ANOVA) was used to test the differences between the mean PEI values of parenchyma, DCIS and IDC [20]. The statistical analyses were performed with BiostaTGV statistical package (BiostaTGV, UMR S 707, INSERM, UPMC, http://marne.u707.jussieu.fr/biostatgv/). In all evaluations, the differences were considered significant if the *p*-value was <0.01.

3. Results

The average tumor size in the group of patients with IDC ($n = 30$) was 1.8 ± 0.4 cm, with the predominant washout time-intensity curve (TIC) in 56.6%, followed by the plateau TIC in 43.4%.

In the group of patients with DCIS ($n = 30$), nonmass-like lesion was present in 14 patients (46.7%) and mass lesions with clumped internal enhancement were present in 16 patients (53.3%). The following kinetic distribution was present: progressive enhancement in 13 patients (43.3%), plateau TIC in 14 patients (46.7%) and washout TIC in 3 patients (10.0%).

The first goal of our study was to define the PEI values for breast parenchyma and for the histologically confirmed lesions: DCIS and IDC. PEI values in breast parenchyma were observed in contralateral healthy breast of all patients ($n = 60$). The values were in range: 55.1–85.5, with the mean value of 70.3 ± 15.2. Intralesional PEI values for histologically confirmed DCIS ($n = 30$) were in range: 403.0–453.0 with the mean value of 428.0 ± 25.0 (Fig. 1), while the values for histologically confirmed IDC ($n = 30$) included the range of values: 716.5–780.9 with the mean value of 748.7 ± 32.2 (Fig. 2).

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