

ORIGINAL ARTICLE

Morpho-dynamic and functional breast MRI features in the assessment of ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) in postmenopausal female patients

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Summary

Introduction: Most frequent histologic types of breast cancer include invasive ductal carcinoma (IDC) and its most common precursor: ductal carcinoma in situ (DCIS). Based on morpho-dynamic and functional parameters: lesion size, initial signal intensity enhancement (wash-in), time-intensity curve (TIC) type, apparent diffusion coefficient (ADC), and positive enhancement integral (PEI), breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) allows the differentiation between IDC and *in situ* lesions in postmenopausal female patients.

Methods: A single-center retrospective study included 40 postmenopausal female patients with histopathologically confirmed diagnosis (DCIS $n_1=20$; IDC $n_2=20$), examined with full diagnostic protocol (FDP) on 1.5T and 3T MRI scanners. The SPSS 21.0 software package was used for the statistical analysis of the defined parameters in two predefined subgroups.

Results: Tumor size was significantly larger ($p<0.001$) in patients with DCIS. The IDC group showed significantly higher wash-in and PEI values ($p<0.001$). ADC was significantly higher ($p<0.001$) in DCIS. There was a statistically significant difference ($p<0.05$) in the TIC type distribution: TIC type 2 was predominant in patients with DCIS, while the TIC type 3 was predominant in patients with IDC.

Conclusion: Based on predefined morpho-dynamic and functional parameters, breast MRI may allow the differentiation between the two types of breast ductal carcinoma: IDC and DCIS. However, histopathological confirmation remains the “golden standard” in differentiation, taking the nature of the disease into account.

Keywords: DCE-MRI, ductal carcinoma in situ, invasive ductal carcinoma, morpho-dynamic parameters, functional parameters



INTRODUCTION

According to the World Health Organization (WHO), breast carcinoma is the most frequent type of cancers in the female population and the most common cause of death by cancer types in female population globally (1). Breast carcinoma predominantly occurs in the female population after the age of 50 (2, 3).

Pathohistologically, breast carcinoma is traditionally divided into non-invasive and invasive types (4). Ductal carcinoma in situ (DCIS) is a heterogeneous disease, which is characterized by the clonal multiplication of epithelial breast cells, that have not yet penetrated the basement membrane (5). The most frequent histological type of breast carcinoma is invasive ductal breast carcinoma (IDC) - the infiltrative malignant neoplasm (4, 6).

Breast magnetic resonance imaging (MRI) is primarily used as the adjunct radiological technique, following mammography and breast ultrasound in the standard patient diagnostic algorithm. MRI is not designed to detect microcalcifications like mammography, however, breast MRI detects 10-15% of additional non-calcified lesions and lesions that are mammographically occult (7, 8). The percentage is even higher in dense breast, taking into account the suboptimal sensitivity of mammography, therefore breast MRI is regarded as the most sensitive imaging technique for breast screening, preoperative staging and therapy monitoring (7-10).

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) represents the advanced diagnostic imaging technique to detect suspicious breast lesions based on the analysis of structural and functional aspects, particularly on postcontrast series, based on the assessment of neoangiogenesis and the lesion microvascularization (8). The additional diagnostic value of DCE-MRI is based on the detection of neoangiogenesis in suspicious lesions, i.e., the increased number and permeability of tumor blood vessels. Following the administration of the contrast agent based on the compounds of gadolinium (Gd), the suspicious lesions tend to express increased permeability, which leads to higher contrast uptake (wash-in) and the subsequent washout (7, 9). Based on the above, the time-intensity (TIC) curve is defined as the increase of the single intensity (SI) and its change against time [s]. Based on the contrast wash-in and washout, it is possible to examine the morphodynamic characteristics of the lesions. DCE-MRI provides high sensitivity, but moderate specificity (7-10). Functional imaging is introduced with the aim of overcoming the moderate specificity: apparent diffusion coefficient (ADC), based on the diffusion-weighted imaging (DWI) and the positive enhancement integral (PEI) values, both representing functional MRI parameters that may further increase the specificity of the exam (9, 10). DWI aims to reflect tissue microstructure changes: the three-dimensional mobility of water molecules, reflect-

ing the organization of the tissue and the ADC [$\text{mm}^2/\text{s} \times 10^{-3}$] allows the quantification of the signal aiming to differentiate between benign and malignant lesions (10). PEI, as the semiquantitative parameter represents the endpoint in tissue perfusion assessment, providing the quantitative information based on the value of extracellular Gd contrast agent in different tissues (9).

The aim of this study is to examine the morphologic aspects: differences in percentage of initial wash-in, time-intensity curve (TIC), apparent diffusion coefficient (ADC), and positive enhancement integral (PEI) in postmenopausal female patients, in order to detect significant and clinically relevant differences in the predefined parameters between DCIS and IDC in postmenopausal female patients with pathohistologically proven diagnosis.

MATERIALS AND METHODS

In this retrospective study, there were 40 postmenopausal female patients, divided into two groups, based on the pathohistological diagnosis: IDC vs. DCIS. The first group (n_1) included 20 postmenopausal female patients, with pathohistologically confirmed pure ductal carcinoma in situ (DCIS). The second group (n_2) consisted of 20 female patients, with pathohistologically confirmed diagnosis of invasive ductal carcinoma (IDC). The MR exams and percutaneous biopsy procedures were conducted in our institution from 2018 to 2022, following the Institutional Review Board decision No 204412-01.

Prior to MRI exam, the initial radiological exam to detect and define the lesions was the full-field digital mammography (FFDM). All mammograms were defined as BI-RADS category 4 or 5. The patients were additionally examined using ultrasound and / or DCE-MRI with DWI in order to define the lesion detectability for the optimal image-guided biopsy procedure. All the lesions were biopsied either by ultrasound-guided core-needle biopsy (US-CNB), or MRI-guided vacuum-assisted biopsy (MR-VAB), or stereotaxic vacuum-assisted biopsy (SVAB). The nature of the lesions was confirmed pathohistologically.

Breast MRI exams in all patients were performed with the MRI-scanners 1.5 T (Avanto fit, Siemens Medical Solutions, Erlangen, Germany) and / or 3 T (Lumina, Siemens Medical Solutions, Erlangen, Germany) with the dedicated bilateral breast coil. Morphodynamic lesion features were defined with the full diagnostic protocol (FDP): T2W and pre- / postcontrast T1W sequences with the DWI with the b-gradients: b_{50} , b_{850} and the generated semiquantitative and ADC maps (10). FDP was used for the axial-plane images (slice thickness 2 mm): T2W STIR (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); T1WFLASH 3D (TE/TR 4.8/9.1, flip angle 25, field of view 340 × 340, image matrix 576 × 564) for 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 gadobutrol (Gadovist, Bayer 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 (9, 10).

Breast MRI exams were analyzed on the dedicated workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany / Carestream Vue PACS, Rochester, NY, USA) using Syngo (Syngo, Siemens Medical Solutions, Erlangen, Germany) and OsiriX (OsiriX, Pixmeo, Geneva, Switzerland) image processing software tools.

The following predefined parameters were computed and analyzed: a.) Lesion size [cm] of DCIS and IDC; b.) Dynamic features (wash-in / washout) were computed as the percentage of the signal intensity (SI) increase within 90 s (wash-in) and the type of time-intensity curve (TIC) was plotted against time [s] (10-12); c.) PEI values were computed as equal to the integral of the area under the curve of the increase in SI after contrast agent injection and expressed in numerical values (13) and d.) ADC values [$\text{mm}^2/\text{s} \times 10^{-3}$] were computed based on the two gradient values on DWI - at b_{50} and b_{850} (10-12).

The data were analyzed using the methods of descriptive and analytical statistics. To compare statistically significant differences between the examined subgroups, we used Chi-square test for the nominal data. Differences between numerical data were compared by Student's t-test or Mann-Whitney U test, depending on the distribution. The difference was considered statistically significant if $p \leq 0.05$, and highly statistically significant if $p \leq 0.001$. The SPSS software package (version 21.0, Chicago, Illinois, USA) was used for data processing.

RESULTS

The female postmenopausal patients in both subgroups (n_1 and n_2) were matched for age: 59,8 +/- 4,6 vs. 60,2 +/- 3,8 ($p=0.767$). The average tumor size (cm) was statistically significantly different between the two subgroups in favor of DCIS ($p < 0.001$), as presented in Table 1. For

dynamic parameters, the wash-in was significantly higher during the first 90 s in the subgroup of patients with IDC ($p < 0.001$). For the functional parameters, both ADC and PEI values were significantly different between the patients with DCIS and IDC ($p < 0.001$), as shown in Table 1.

Regarding the distribution of the TIC: there was the predilection for the TIC type 2 in the subgroup of patients with DCIS and for the TIC type 3 in the subgroup of patients with IDC, as shown in Table 2.

Table 2. Distribution of TIC types in n_1 and n_2 .

TIC type	Subgroup		p
	n_1	n_2	
Type 1	3	4	0.004*
	15.0%	20.0%	
Type 2	14	4	
	70.0%	20.0%	
Type 3	3	12	
	15.0%	60.0%	

* Statistically significant difference ($p \leq 0.05$)

Based on the above, the postmenopausal female patients with higher initial wash-in values, TIC type 3 and lower values for ADC, with higher values for PEI, tend to belong to the group of patients with IDC (Figure 1), while the patients with lower wash-in values, TIC type 2 and the higher values of ADC and lower values of PEI, tend to belong to the group of patients with DCIS (Figure 2).

DISCUSSION

Breast MRI has long been a radiological method, which tended to overcome its moderate specificity with the introduction of the functional aspects in order to distinguish between the clinically relevant criteria: benign vs. malignant, responder vs. non-responder, in situ vs. invasive, etc. So far, large studies have tended to qualify and quantify the parameters of morphology, dynamic features and functional aspects separately and as groups of parameters with scores, having in mind radiological – pathological correlations, as the “golden standard” of assessment. The compound scores, sometimes related to as the “virtual biopsy” were supposed to lower the number

Table 1. Patient age (years), lesion size (cm), wash-in (% / 90s) positive enhancement integral value (PEI value) and apparent diffusion coefficient (ADC, [$10^{-3}\text{mm}^2/\text{s}$]).

Group	n_1	n_2	p
Age (years)	59.8 +/- 4.6	60.2 +/- 3.8	0.767
Lesion size (cm)	2.7 +/- 0.7	1.6 +/- 0.2	<0.001*
Wash-in (%/90s)	165.0 [96.0 – 345.0]	255.0 [145.0 – 452.0]	<0.001*
ADC ($10^{-3}\text{mm}^2/\text{s}$)	1.32 +/- 0.05	1.09 +/- 0.11	<0.001*
PEI values	435.0 [235.5 – 688.7]	1000.2 [654.2 – 1680.4]	<0.001*

* statistically significant difference ($p \leq 0.001$)

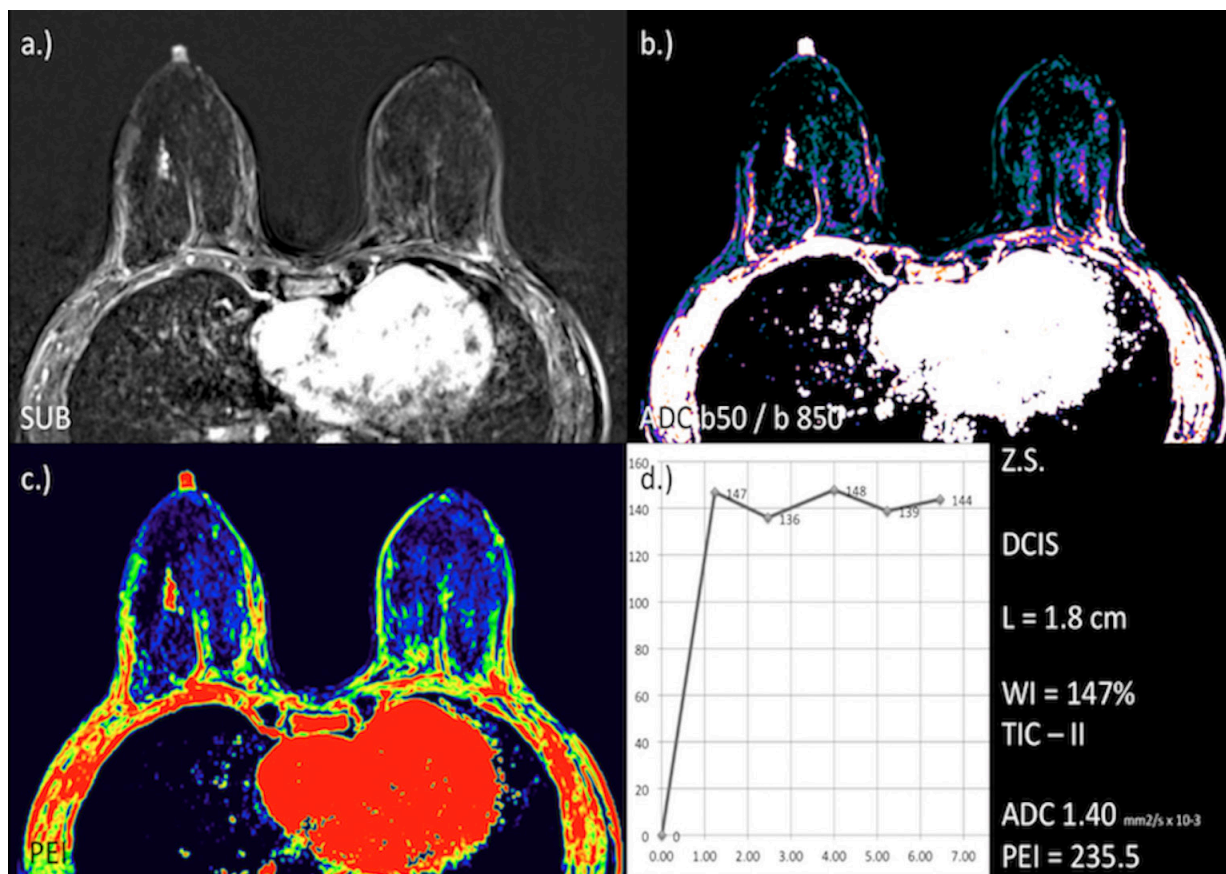


Figure 1. Morpho-dynamic and functional parameters of a 64-yr. old patient (Z.S.) with DCIS. (a) DCE-MRI, Subtraction (b) Diffusion Coefficient (ADC). (c) Positive Enhancement Integral (PEI). (d) Time-intensity curve.

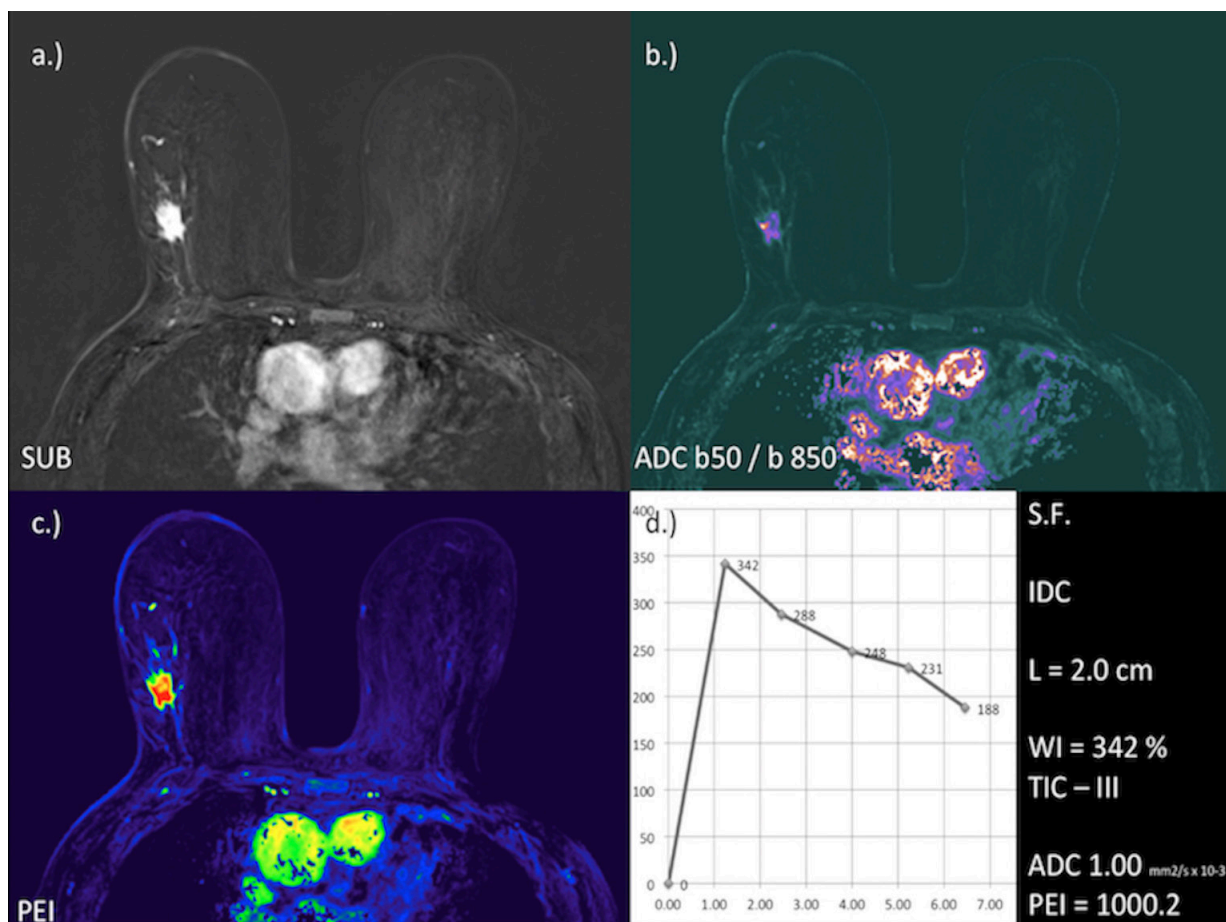


Figure 2. Morpho-dynamic and functional parameters of a 62-yr. old patient (S.F.) with IDC. (a) DCE-MRI, Subtraction (b) Diffusion Coefficient (ADC). (c) Positive Enhancement Integral (PEI). (d) Time-intensity curve.

of the overdiagnosed patients with unnecessary biopsies, confirming the benign nature of the disease. Additional scores, which introduced the algorithms (notably Fischer / Goettingen, and Kaiser score), aimed to define whether the lesion was suspicious based on the morphologic and dynamic features additionally with the use of DWI-ADC (14, 15). In our research, we tried to define the morpho-dynamic features routinely assessed in the breast MRI exam, with the addition of two functional parameters aiming to cover different aspects of carcinogenesis: neoangiogenesis with contrast-enhanced MRI, kinetics of the contrast medium, with the assessment of dynamic parameters, lesion perfusion features with PEI and tissue organization and level of cellularity with DWI-ADC (9-12).

Female patients in the two subgroups were matched for age, all being postmenopausal with pathohistologically confirmed lesions. In terms of morphology, we decided to compare the lesion size with the largest diameter, as the general idea was not to include the bulky tumors and locally advanced tumors, taking into account the specific growth perturbation in these tumors. Concerning the lesion morphology, the DCIS tend to show different levels of heterogeneity, however, the malignant lesions larger than 2 mm, produce growth factors stimulating angiogenesis and neoangiogenesis (16). This explains the increase in SI, as early as within the first two minutes following the contrast medium application (10, 16, 17). In our study, we obtained statistically significant higher wash-in values in the group of patients with pathohistologically confirmed IDC compared to the group with pathohistologically confirmed DCIS.

Jensen et al. reported results consistent with those obtained in this study regarding the TIC: TIC type 2 is most frequently detected in DCIS (18). There are studies that proved no regularity in TIC assessment (19). Our results confirm that TIC type 3 is more common in IDC, which was also confirmed in other studies (20-22). However, regarding the available references, there is no sufficiently defined data regarding the comparison of the predominant curve type in DCIS and IDC. We also need to mention that the heterogeneity may contribute to the lack of the common conclusion, taking into account the fact that the more heterogeneous lesions contain the pixels which do not necessarily show the enhancement, therefore the region of interest may include the areas of the normal tissue, fibrocystic changes, in situ and or invasive areas, leading to the lack of TIC type specificity. The results of this study confirm the expected predominance of the type 2 in DCIS and type 3 in IDC, which is consistent with the malignant potential of invasive carcinoma and its infiltrative growth (4).

Expectedly, the tissue microstructure changes in more proliferative lesions, with higher level of cellularity, leading to the reduced water molecule thermal movements, which served as the basis for the application of DWI-ADC in oncologic imaging: the more malignant the lesions

tend to be, the lower their ADC values become (21-23). It is worth mentioning that the ADC is considered to be the marker of cellularity (24). This specifically allows us to differentiate the lesions according to the grade: low vs. high grade DCIS, and DCIS vs. IDC (25-28). Our data confirmed that the ADC is significantly higher in DCIS compared to IDC (24-27). Based on this, the ADC increases the positive predictive value of breast MRI up to 96.6% and the specificity up to 93.3% (29).

Unlike mammography, DCE-MRI has greater sensitivity to determine the size of the DCIS lesion. The DCIS detectability relies on periductal and stromal vascular elements (30-33). The features of tissue perfusion, in addition to morphological criteria, may provide additional data about the underlying process and may contribute to better differentiation between in situ and invasive diseases. The sensitivity of DCE-MRI for the detection of DCIS ranges from 77 to 96% (30-33).

PEI values, as the integral part of the standardized DCE-MRI exam, give insight into the tissue perfusion and may contribute to better lesion characterization (9, 13, 31, 32). As a heterogeneous lesion, DCIS often appears as the non-mass enhancement (NME), with variable distribution and enhancement patterns. SI in DCIS may remain below the SI threshold typical for invasive carcinomas, which may also underestimate the extension of the lesion (14, 30-33). Based on the previous research in the field, we expected the degree of perfusion would be different in DCIS compared to IDC, which the results of this study confirmed (9). The PEI values in IDC were significantly higher compared to those in DCIS ($p < 0.001$).

Our study has certain limitations: it is a single-center retrospective study. The relatively small number of patients certainly does not contribute to the generalized conclusions. However, the single-center study, contributes to the evaluation of the results based on uniform diagnostic protocols and the same technical conditions, which leads to standardized approach and better reproducibility. With the postmenopausal female patients in the study, the effects of hormonal changes were eliminated. Due to the limited number of subjects, it was not possible to define MRI parameters according to histological grades, however these data may serve as the basis for the prospective multicentric trial, aiming to differentiate between the histological grades and the criteria defined by immunostaining, which are related to the treatment selection.

CONCLUSION

The pre-defined morpho-dynamic and functional parameters in breast MRI, provide additional information in differentiation between invasive and in situ ductal breast carcinomas. The potential use of the additional parameters (DWI-ADC and PEI) in routine breast MRI

protocols may be of help in differentiation between DCIS and IDC, potentially increasing the specificity of MRI.

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None.

Conflicts of interest

None to declare.

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MORFO-DINAMSKE I FUNKCIONALNE KARAKTERISTIKE MRI DOJKI U PROCENI DUKTLANOG KARCINOMA IN SITU I INVAZIVNOG DUKTALNOG KARCINOMA KOD POSTMENOPAUZALNIH ISPITANICA

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Sažetak

Uvod: Najčešći histološki tipovi karcinoma dojke podrazumevaju invazivni duktalni karcinom (IDC), kao i njegov najčešći prekursor – duktalni karcinom in situ (DCIS). Evaluacija morfo-dinamskih i funkcionalnih parametara na MRI dojki: veličina lezije, inicijalno postkontrastno povećanje intenziteta signala (wash-in), definisanje tipa krive promene intenziteta signala u jedinici vremena (TIC), koeficijent difuzije (ADC), kao i procena pozitivne vrednosti integrala postkontrastnog povećanja intenziteta signala kod postmenopauzalnih ispitanica, omogućavaju diferencijaciju između IDC i in situ lezije.

Metode: U retrospektivno ispitivanje sprovedeno u jednom centru, uključeno je 40 postmenopauzalnih ispitanica sa potvrđenom histopatološkom dijagnozom (DCIS $n_1=20$; IDC $n_2=20$), kod kojih su analizirane lezije na MRI dojki sa primenom standardnog - kompletnog dijagnostičkog protokola na apartima 1.5T i 3T. Softverski paket

SPSS 21.0 je korišćen u statističkoj analizi – proceni razlike predefinisanih parametara u dve grupe ispitanica.

Rezultati: Veličina tumora je bila statistički značajno veća ($p<0.001$) kod ispitanica sa DCIS. U podgrupi ispitanica sa IDC, postoji statistički značajna razlika – veće vrednosti “wash-in” i PEI ($p<0.001$). Vrednost ADC je bila statistički značajno veća u grupi ispitanica sa DCIS ($p<0.001$). Postoji i značajna razlika u distribuciji TIC ($p<0.05$): TIC tip 2 je najviše zastupljena kod ispitanica sa DCIS, dok je TIC tip 3 dominantno zastupljena kod ispitanica sa IDC.

Zaključak: Na osnovu predefinisanih morfo-dinamskih i funkcionalnih parametara, MRI dojki može da omogućiti diferencijaciju između dva tipa duktalnog karcinoma: IDC i DCIS. Histopatološka potvrda ostaje „zlatni standard” u diferencijaciji, uzimajući u obzir prirodu bolesti..

Ključne reči: MRI dojki, duktalni karcinom in situ, invazivni duktalni karcinom, morfo-dinamski parametri, funkcionalni parametri

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