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MRI in the evaluation of breast cancer patient response to neoadjuvant chemotherapy: predictive factors for breast conservative surgery

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PURPOSE
We aimed to prospectively assess the role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in the evaluation of predictive factors for breast conservative surgery during neoadjuvant chemotherapy.

MATERIALS AND METHODS
Sixty-six patients were evaluated before the first treatment cycle, after the second cycle, and upon the completion of neoadjuvant chemotherapy according to largest tumor diameter, tumor volume, postcontrast enhancement, and tumor regression pattern. The patients were divided into responders (pathologic complete and near complete response) and nonresponders. Each subgroup was re-evaluated according to morphokinetic criteria for identification of candidates for breast conservative surgery.

RESULTS
In responders (n=27), the lesion size upon the completion of neoadjuvant chemotherapy was significantly smaller compared to nonresponders (1.5±0.6 vs. 3.2±0.9 cm; $P < 0.001$), as was the volume (1.2 vs. 11.0 cm^3; $P < 0.001$). The measured lesion size did not differ from the histologic size (1.5±0.6 vs. 1.2±0.6 cm; $P = 0.09$) and had a high correlation (r=0.93). In responders, the following parameters were significantly different before and after neoadjuvant chemotherapy: size (3.6±1.4 to 1.5±0.6 cm; $P < 0.001$), volume (17.6 to 1.2 cm^3; $P < 0.001$), predominant concentric regression, plateau and continuous time-intensity curves ($P < 0.001$). DCE-MRI has the sensitivity of 87% and the accuracy of 77% to identify candidates for breast conservative surgery.

CONCLUSION
Selected morphokinetic DCE-MRI parameters may contribute to the multidisciplinary decision when considering the selection of candidates for breast conservative surgery.

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Neoadjuvant chemotherapy (NACT), the systemic preoperative treatment, is recommended in patients with locally advanced breast cancer and in patients with operable cancer who were not considered candidates for breast conservative surgery (1). Recent published references based on large clinical trials suggest that relapse-free survival and overall survival outcomes in patients treated with adjuvant and neoadjuvant treatments are equivalent (2, 3). The tumors undergo radiological evaluation with dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), with the aim of documenting the response to NACT in terms of distinction between the responders and nonresponders, thereby determining nonresponders as early as possible to offer them another treatment modality.

NACT offers several advantages: tumor size reduction, earlier treatment of micrometastases, assessment and early prediction of tumor response, all allowing the achievement of the pathological complete response (pCR). pCR is defined as the specific surrogate endpoint for survival outcome to recommend breast conservative surgery instead of mastectomy in selected cases (1, 4, 5). The aim of breast conservative surgery is long-term disease control through excision of all of invasive and *in situ* cancer. Breast conservative surgery is as effective as mastectomy in terms of overall survival, ensures a good cosmetic result, and has many advantages in terms of psychological effects and quality of life (6, 7). Surgical criteria for patient selection for breast conservative surgery include the following parameters: tumor extent, presence of unifocal tumors relative to the size of the breast ("tumor size to breast volume" ratio), tumor location, and patient preference (6, 8). Clinicopathological criteria also determine the suitability of patients for undergoing breast conservative surgery. Risk factors for failure are margin status, including the extent of the margin involvement, young age and an extensive intraductal component (9, 10). The pathologic margin status is considered the most important factor for recurrence, influencing the choice of surgical treatment modality (11, 12). Although the margin status and the presence of an extensive *in situ* component remain the key determinants of disease recurrence, the same applies for tumors larger than 2 cm in size (13). There is no data concerning the safety of breast conservative surgery for the surgical treatment of invasive tumors larger than 4 cm in size (13, 14). Radiotherapy is generally recommended after breast conservative surgery, reducing the risk of recurrence by approximately one half (15).

Clinical examination, mammography, and ultrasound have limited value in tumor response evaluation (16–18). DCE-MRI precisely defines the disease extent through selected morphokinetic parameters and is

considered a good pCR discriminator regardless of the tumor subtype. DCE-MRI provides good correlation, even in cases of lobular carcinoma, multifocal and multicentric disease, allowing for early dynamic and metabolic assessment of tumors: tumor morphology changes, regression and enhancement patterns, and tridimensional and volume evaluation, which all define a specific "MRI phenotype" (19–22). The morphokinetic features in DCE-MRI examinations are based on recommended oncologic imaging measurement tools (19–22).

The goal of this prospective radiological cohort study was to evaluate the role of DCE-MRI in the follow-up of patients with locally advanced breast cancer given NACT to define radiologic factors that would be predictive for patient selection for breast conservative surgery, according to histologic criteria.

Materials and methods

Seventy patients were originally included in this study. All patients were diagnosed with histologically confirmed locally advanced breast cancer after either fine-needle aspiration biopsy, Tru-cut biopsy, or incisional biopsy, all mammographically examined after the histologic verification and staged as BI-RADS 6 prior to inclusion in the trial (23). The DCE-MRI follow-up of patients given NACT was performed at the Institute of Oncology and Radiology of Serbia between January 2010 and September 2012 following the Institutional Review Board approval. All patients gave written informed consent to participate in the trial. Apart from the histological verification of the invasive breast carcinoma, the inclusion criteria comprised the presence of a measurable lesion, according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1); patient performance status defined as less than 2, according to the Eastern Cooperative Oncology Group (ECOG) performance status grade; or the Karnofsky index higher than 60%. The exclusion criteria comprised the detection of visceral metastases prior to or in the course of NACT and primary inflammatory carcinoma. All patients were radiologically evaluated prior to the beginning and after the fourth cycle of NACT by chest X-ray or contrast-enhanced computed tomography, abdominal ultrasonography and bone scan. The lesions were classified according to the TNM classification system as T2–T4, i.e., the American Joint Committee on Cancer (AJCC) stage groups IIB, IIIA and IIIB (24). NACT in all patients consisted of anthracycline-based regimens: 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide every two weeks for four cycles intravenously followed by weekly 80 mg/m^2 paclitaxel or dose-dense doxorubicin-cyclophosphamide followed by paclitaxel every two weeks (25).

The patients were assessed three times with DCE-MRI. The first examination was less than one week prior to beginning NACT, the second examination was within two weeks after the second cycle of NACT, and the third examination was after the completion of NACT and less than two weeks before the surgical treatment. All examinations were performed with a 1.5 Tesla MRI unit (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) with dedicated bilateral breast specific coil and the patient in the prone position. The standard protocol was used for the axial-plane images with the slice thickness of 2 mm, as shown in Table 1.

After the native series of dynamic T1-weighted FLASH images, the contrast medium was applied: the bolus injection of 0.1 mmol/kg body weight of gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma, Berlin, Germany) was injected with the automatic injector (Mississippi, Ulrich Medical, Ulm, Germany) at the rate of 2 mL/s, followed by the flush of 20 mL saline. Contrast-enhanced dynamic sequences were acquired five times every 1 min 23 s. Subtraction (pixel-by-pixel), maximum intensity projection, multiplanar reconstruction, and volume rendering technique were performed in the postprocessing with the use of image processing software and the DICOM viewer OsiriX (OsiriX, Pixmeo, Geneva, Switzerland). Tumor kinetics was analyzed based on semiquantitative analysis of gadolinium contrast uptake with the free-hand selected region of interest based on the choice of the parametric wash-in color map; areas of maximum enhancement and time intensity curves (TICs) matching enhancement (%) against time (s) were created on the workstation Leonardo, using the image processing software Syngo (Syngo, Siemens Medical Solutions).

For each of the three DCE-MRI examinations, lesions were assessed according to the following criteria:

1) Response evaluation criteria in solid tumors, version 1.1 (RECIST 1.1): the unidimensional measuring tool, defining and further evaluating the largest tumor diameter (cm) or the sum of the target lesions largest diameters (cm), with the follow-up response evaluated according to the response categories (26).
2) Tumor volume (cm^3): software-based tumor volume calculation on the initial and subsequent examinations, using the ellipsoid formula, which takes into consideration the

Table 1. Standard DCE-MRI protocol for axial-plane images for T1-weighted FLASH 3D native and five postcontrast series

MRI sequence/parameters	T2-weighted TIRM	T1-weighted TSE	T1-weighted TSE	T1-weighted FLASH 3D
Echo time (ms)	60	70	12	4.8
Repetition time (ms)	7690	5900	910	9.1
Inversion time (ms)	180			
Flip angle (°)	150	180	90	25
Field of view (mm×mm)	340×340	340×340	340×340	340×340
Image matrix	320×256	384×319	320×234	576×564

3D, three-dimensional; FLASH, fast low-angle shot pulse sequence; TIRM, turbo inversion recovery magnitude; TSE, turbo spin-echo.

three dimensions of the tumor: V=Pi/6 (length)×(width)×(height) (27); the 65% volume decrease was considered the threshold limit for response after the second cycle and the 83% volume decrease upon completion of NACT (5, 28).

3) Tumor regression pattern, where the concentric tumor regression is considered the favorable pattern for breast conservative surgery (1).
4) TIC (%/90 s) and the change of the shape of the curve in the delayed phase towards curve flattening, which is considered favorable (1).

The selected MRI parameters were then tested against the histopathological findings. After the surgery, the tumors were measured in three dimensions to provide consistency with the radiologic measurements and the most accurate volume calculation. Breast carcinomas are considered three-dimensional solid tumors, with the volume calculated based on the equation: V=π/6 (length)×(width)×(height) (27, 29). Based on the histopathological findings, the two subgroups were created: responders and nonresponders. The responders are defined as the patients achieving pCR and near-pCR, according to the criteria proposed by Kuerer et al. (30). The responders included the patients with the tumors completely eliminated upon the completion of NACT, based on histologic assessment (pCR) and those achieving the near-complete pathologic tumor response (near-pCR) with the residual tumor volume ≤1 cm^3 (30). Both pathologic categories, pCR and near-pCR, are considered to be in the same prognostic category (26, 28–32). In addition to the histologic criteria, these patients are considered the candidates for breast conservative surgery, provided that their nodal status permits breast conservative surgery, as was the case in all patients classified as responders.

Statistical analysis

The distinctive MRI features discussed above were analyzed and compared for each subgroup, thus defining the MRI-features of histologic responders. The nonparametric two-tailed Mann-Whitney U test was performed for the comparison of responders and nonresponders. The *P* value of 0.05 or less, or when possible 0.01 or 0.001, was considered significant. The Spearman's rank correlation coefficient was also calculated (33). The two-tailed Fisher's exact test was chosen for categorical variables.

Table 2. Patient and tumor characteristics

	Result
Number of patients	66
Age (years), *mean±SD (range)*	53.2±9.5 (32–77)
Initial T (TNM classification), *n (%)*	
T2 (2–5 cm)	46 (69.7)
T3 (>5 cm)	18 (27.3)
T4 (any size with direct extension to chest wall or skin)	2 (3)
AJCC stage groups, *n (%)*	
IIB (T2, N1, M0 or T3, N0, M0)	55 (83.3)
IIIA (T2, N2, M0 or T3, N1, M0 or T3, N2, M0)	9 (13.6)
IIIB (T4, any N, M0 or any T, N3, M0)	2 (3)
Histological subtype, *n (%)*	
IDC	56 (83.3)
ILC	10 (16.7)
Pathologic response, *n (%)*	
Complete (pCR)+near complete (≤1 cm^3)	27 (40.9)
Incomplete	39 (59.1)

AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; pCR, pathologic complete response; SD, standard deviation; TNM, classification of malignant tumors (T, tumor; N, lymph node; M, metastasis).

Results

Patients

Seventy patients were enrolled in the trial according to the inclusion criteria. During the first four cycles of NACT, the distant metastases were detected in three patients, and one patient changed the place of residence and the referring institution. After the exclusion of these four patients, 66 patients completed NACT and all three DCE-MRI examinations as scheduled in the protocol (Fig. 1). Patient demographic and tumor characteristics are summarized in Table 2.

DCE-MRI evaluation of tumor response to NACT

In the group of 66 patients, all tumors were measurable according to RECIST 1.1. The average size of the target lesion decreased from 4.3±1.6 cm on the initial exam to 3.5±1.5 cm after the two cycles ($P < 0.01$) and to 2.5±1.5 cm upon the completion of NACT ($P < 0.001$). According to the response categories proposed by RECIST 1.1, there were 52 patients who had stable disease, 13 patients with partial response, and one patient with progressive disease. After the completion of NACT, one patient achieved radiologic complete response and 45 patients achieved partial response, altogether resulting in 46 responders (69.7%) and 20 stable disease patients (30.3%). The difference between the assessment categories after the second cycle and upon the completion of NACT was highly significant ($P < 0.001$).

The average target lesion volume was initially 32.2 cm^3 compared to 17.1 cm^3 after the two cycles ($P < 0.01$) and 4.9 cm^3 after the completion of NACT ($P < 0.001$). The average target lesion volume decreased by 46.9% after the two cycles of NACT, which was below the threshold limit of 65% volume decrease for response, and decreased by 84.8% upon the completion of NACT,

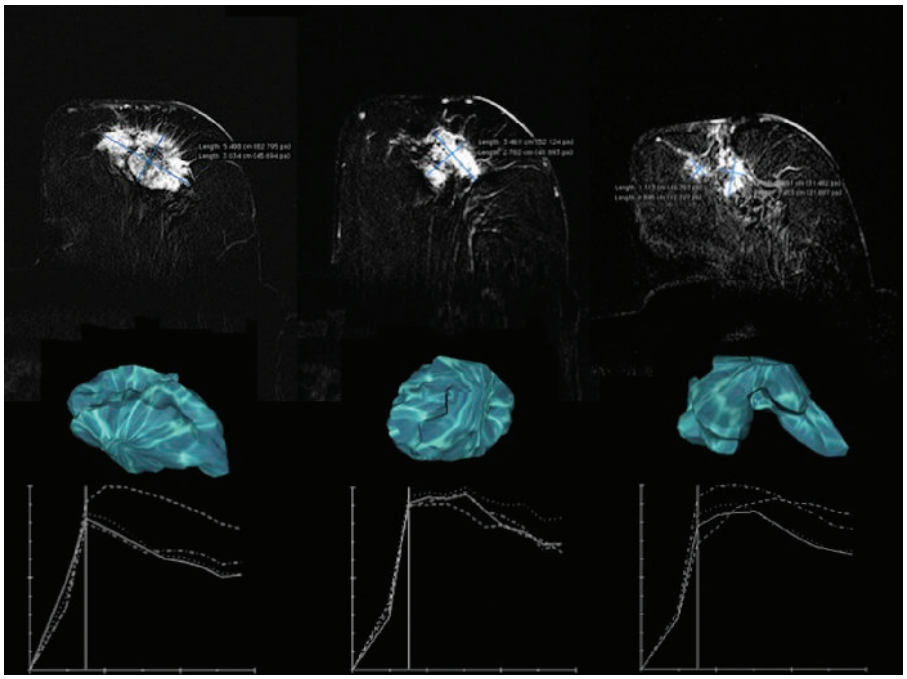

Figure 1. DCE-MRI. Analysis of a patient on three scheduled MRI examinations. Initial target lesion size was 5.5 cm. After the two cycles of neoadjuvant chemotherapy (NACT), the lesion decreased by 38.2% and upon the completion, the lesion decreased by 41.8%. The initial volume of 41.1 cm^3 decreased by 63.8% after the second cycle of NACT and by 90.5% after the completion of NACT. The regression pattern after the doxorubicin-cyclophosphamide regimen was concentric. After the taxane-based chemotherapy, the tumor regression pattern was dendritic. Following the washout time intensity curve, the curve-flattening phenomenon occurred after the two cycles and upon the completion of NACT.

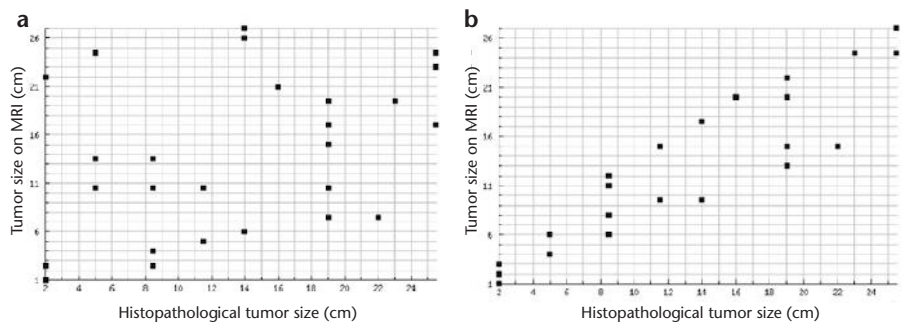

Figure 2. a, b. Correlation between tumor size on MRI examination (RECIST) and histopathological tumor size after two cycles of NACT (r=0.38; 95% confidence interval, 0–0.66; $P = 0.02$) **(a)** and upon the completion of NACT (r=0.93; 95% confidence interval, 0.85–0.97; $P < 0.0001$) **(b)** in patients with pCR and near-pCR (n=27).

which was above the predefined 83% cut-off value for response.

After the second cycle of NACT, the concentric regression pattern was noted in 60 lesions (90.9%), and upon the completion of NACT, the same pattern was noted in 51 lesions (77.3%) ($P = 0.03$).

Before the initial course of NACT, the washout curve type was predominant (42 patients, 63.4%), followed by the plateau TIC (24 patients, 36.6%). After the second cycle of NACT, the number of patients with the initial washout TIC decreased to 27 (40.9%), with the curve-flattening phenomenon occurring in 37 patients (56%). Two patients, who originally belonged to the plateau TIC type, had progressive contrast enhancement after the second cycle of NACT. The difference in TIC distribution in patients was significant after the second cycle of NACT ($P = 0.01$). After the completion of NACT, six patients (9.1%) had the unchanged washout curve, whereas 45 patients (68.2%) had the plateau curve type, and 15 patients (22.7%) had the progressive delayed enhancement ($P < 0.001$).

Analysis of patients with histologic response

The responders (defined as pCR and near-pCR) included 27 patients from the original group of 66 patients (40.9%), with three patients (4.54%) achieving pCR and 24 patients (36.4%) achieving near-pCR.

The average size of the target lesion (RECIST 1.1) on the initial pre-NACT DCE-MRI examination was 3.6±1.4 cm compared to 2.7±1.5 cm after the two cycles of NACT ($P < 0.01$) and 1.5±0.6 cm after the completion of NACT ($P < 0.001$). After the two cycles of NACT, 16 patients had stable disease, 10 patients had partial response, and one patient had progressive disease. After the completion of NACT, one patient achieved complete response and 25 patients achieved partial response, making altogether the 26 radiologic responders (96.3%). There was no significant difference between the radiologic tumor size upon the completion of NACT and the histopathological tumor size (1.5±0.6 cm vs. 1.2±0.6 cm; $P = 0.09$) with the high correlation coefficient (r=0.93) (Fig. 2).

The average tumor volume was initially 17.6 cm^3 compared to 7.7 cm^3 after the two cycles of NACT ($P = 0.001$) and 1.2 cm^3 after the completion of NACT ($P < 0.001$). The average volume decreased by 56.2% after the two cycles of NACT (below the predefined threshold limit for response) and by 93.2% after the completion of NACT (above the predefined threshold limit for response). The correlation coefficient between the volume defined by MRI examination upon the completion of NACT and the histopathological size was high (r=0.89) (Fig. 3). The differences between the tumor size and volume in responders and nonresponders are summarized in Table 3.

There were 24 lesions (88.9%) with concentric regression pattern after the second cycle of NACT and 25 lesions (92.6%) after the completion of NACT ($P = 0.68$). Before the initial course of NACT, there were 14 patients (51.8%) with the plateau TIC, 13 patients (48.2%) with the washout TIC and no patients with the continuous TIC. As early as after the second cycle of NACT, the number of patients with the washout TIC decreased to eight, two patients had progressive contrast

enhancement and the remaining seventeen had the plateau TIC ($P = 0.15$). After the completion of NACT, no patients had the washout curve type, 15 patients (57.7%) had the plateau and 11 patients (42.3%) had the continuous postcontrast enhancement; one patient achieved the radiological complete response without any detectable lesion in the DCE-MRI study ($P < 0.001$), as presented in Table 4.

The sensitivity and specificity for responder identification after the second cycle of NACT, based on pure morphokinetic features on DCE-MRI examination, were 93% and 40%, respectively. Positive and negative predictive values (PPV and NPV) were 72% and 77%, and the rate of false positive findings was 23%. The sensitivity and specificity upon the completion of NACT were 87% and 63%, respectively, with the PPV and NPV of 73% and the rate of false positive findings of 15%.

Analysis of nonresponders

In nonresponders (n=39), the target lesion size between the first and second MRI examinations had no significant difference (4.8±1.6 vs. 4.1±1.2 cm; $P = 0.065$). Upon the completion of NACT, the target lesion size decreased (4.8±1.6 vs. 3.2±0.9 cm; $P < 0.01$). Although the change in size was statistically significant, nearly one half of the patients remained in the stable disease category (n=19, 48.7%), while the other 20 nonresponders achieved partial response. The same applied for the volume change, with the marginal difference in the early response evaluation ($P = 0.03$). The increased number of nonresponders had dendritic tumor regression upon the completion of NACT (35.9%; $P = 0.006$).

Discussion

In tumor response evaluation to NACT, DCE-MRI was confirmed to be superior to clinical examination, mammography or ultrasound and has become the recommended imaging modality of choice (34). This was recently confirmed by the results of the large multicentric clinical trial (ACRIN 6657) by Hylton et al. (2). Numerous clinical trials tested the use of DCE-MRI in tumor response evaluation to NACT, testing the predefined morphologic criteria as the surrogate endpoints for the OS (1–3, 5, 16, 17, 20–22, 33, 35). However, the role of DCE-MRI in planning breast conservative surgery has not been widely discussed in radiology. The majority of the existing papers deal with the surgical endpoints, older versions of RECIST, mainly without the thorough analysis of multiple morphokinetic DCE-MRI criteria (36). The clinical relevance of DCE-MRI in presurgical planning after the completion of NACT has been emphasized in the position paper of the European Society of Breast Cancer Specialists (EUSOMA) regarding the poor shift from mastectomy to breast conservative surgery upon the completion of NACT, related to the general surgeons' attitude for aggressive approach despite the DCE-MRI confirmed tumor response to NACT (37). Therefore, our study aimed to analyze the four DCE-MRI parameters (tumor size according to RECIST 1.1, tumor volume, regression pattern, and TIC) as the radiologic predictive factors for breast conservative surgery planning upon the completion of NACT.

According to the systematic analysis of the 16 clinical trials, which tested

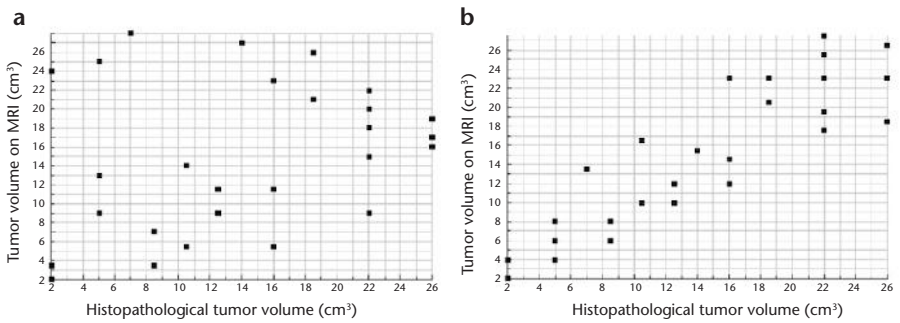

Figure 3. a, b. Correlation between tumor volume on MRI examination (cm^3) and histopathological tumor size after the two cycles of NACT (r=0.28; 95% confidence interval, -0.1–0.60; $P = 0.07$) **(a)** and upon the completion of NACT (r=0.89; 95% confidence interval, 0.77–0.95; $P < 0.0001$) **(b)** in responders (n=27).

Table 3. Differences in tumor size and volume between responders and nonresponders initially, during, and after NACT and histopathological findings

Examination/parameter		Responders (pCR+near-pCR)	Nonresponders	*P*
Age (years)		53.5±10.9	53.0±8.2	0.89
Initial pre-NACT	RECIST, size (cm)	3.6±1.4	4.8±1.6	< 0.001
	Volume (cm^3)	17.6	42.4	< 0.001
After two cycles of NACT	RECIST, size (cm)	2.7±1.5	4.1±1.2	< 0.001
	Volume (cm^3)	7.7	23.7	< 0.001
Post-NACT	RECIST, size (cm)	1.5±0.6	3.2±0.9	< 0.001
	Volume (cm^3)	1.2	11.0	< 0.001
Histopathological findings	Size (cm)	1.2±0.6	2.9±0.9	< 0.001
	Volume (cm^3)	0.5	7.8	< 0.001

NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; RECIST, Response Evaluation Criteria in Solid Tumors.
Data are given as mean or mean±standard deviation.

Table 4. Type of time-intensity curve in responders

Type of TIC, *n (%)*	Continuous	Plateau	Washout
Initial	0 (0)	14 (51.8)	13 (48.2)
After two cycles of NACT	2 (7.4)	17 (62.9)	8 (29.6)
Post-NACT	11 (42.3)	15 (57.7)	0 (0)

NACT, neoadjuvant chemotherapy; TIC, time-intensity curve.
After the completion of NACT, one out of 27 patients achieved the radiologic complete response with the complete tumor regression; the subanalysis was performed for all visible tumors in the subgroup (n=26).

the role of DCE-MRI in the evaluation of tumor response to NACT from 1994–2010 (n=587), the efficacy of DCE-MRI was proven in the follow-up and evaluation of tumor response and the methodological heterogeneity was noted concerning the different NACT and DCE-MRI protocols and the different timeline of examinations (3). The first part of our prospective study included the DCE-MRI evaluation of 66 patients in three stages, i.e., before the beginning, after the second cycle, and upon the completion of NACT, according to the diagnostic protocol used in our institution. The validity of our DCE-MRI protocol has been confirmed through the statistically significant changes of the pre-defined parameters, which was considered the prerequisite for the second part of the study.

The second part of the study included the division of the whole group into two subgroups (responders vs. nonresponders) according to histologic criteria and re-evaluation of the predefined morphokinetic parameters in responders. The hypothesis was that the subgroup of patients with pCR and near-pCR would have the representative DCE-MRI parameters for breast conservative surgery.

Unidimensional response evaluation according to RECIST 1.1 has shown that statistically significant tumor response was achieved as early as after the second cycle of NACT and, more significantly, upon the completion of NACT, which is in accordance with the RECIST 1.1 categories, with 26 patients (96.3%) achieving partial or complete response upon the completion of NACT. The high correlation was proven between the radiologic size upon the completion of NACT and the histologic size (r=0.93). The tumor size is not only the independent prognostic factor, but also the assessment tool for response evaluation to NACT (35, 38), which is considered the significant and independent predictor of histologic response. The largest tumor dimension change is directly proportional to the logarithmic value of the number of cells killed by the standardized dose of NACT (26, 39). This relation served as the basis for the use of DCE-MRI and measurements, according to RECIST 1.1 in the identification of the patients for breast conservative surgery.

In our study, the tumor volume was calculated based on the three tumor dimensions. The volume changed after the two cycles of NACT and upon the completion of NACT. The correlation coefficient between the radiologic volume upon the completion of NACT and the histopathological size was high. RECIST 1.1 does not precisely define the role of the volume measurement or the mathematical model (38). The volume being used as the endpoint still remains an open issue. Assuming that the tumor is not an ideal sphere, the volume was defined with the three tumor dimensions. During the early growth, the tumor growth perturbation decreases and both, the growth and perturbation are defined with the mathematical expression of the dependence of tumor size over time (40). Later in tumorogenesis, the perturbation in growth increases and the tumor becomes flattened or ellipse shaped (40). Based on these assumptions and previous references by Wapnir et al. (29) for locally advanced breast cancer, we selected the ellipsoid volume formula for both radiological and pathological volume calculations in our study as the best feasible approximation (27, 29, 41). According to Shin et al. (41), the tumor volume analysis based only on the largest diameter for the volume calculation overestimates the tumor volume and poorly reflects the true volume of the tumor. With the sensitivity of 93% of the DCE-MRI examination after completion of the second cycle of NACT in our group, based on the 65% volume decrease cut-off, the responders could be identified with DCE-MRI as early as after the second cycle of NACT, which favors the volume calculation based on three diameters for the patient identification and selection for breast conservative surgery.

It should also be mentioned that the patients with histologic response initially had the smaller tumor size and volume than the nonresponders. Although the average tumor size and volume change in the responders compared to the nonresponders over the course of NACT were statistically significant, the significance of the volume change was prominent upon the completion of the treatment.

TIC flattening typically observed in responders (42) and the concentric regression pattern have shown the significant difference between responders and non-responders, which apart from response prediction, served as discriminating factors for determining whether breast conservative surgery was suitable. Concentric tumor regression has already proven to be the predictive factor for the selection of candidates for breast conservative surgery because of the negative tumor margins, thus enabling breast conservative surgery (43).

Our study is limited by the relatively low number of participants, particularly for the analysis of responders; therefore, further research is needed. The study was designed as the purely radiologic evaluation with the correlation to histologic evaluation as the highest standard. Large clinical trial, designed to follow patients with different types of surgery and pathologic criteria over time, is necessary to provide answers concerning the overall survival in patients with breast conservative surgery. Although the DCE-MRI identifies the responders, the final decision concerning the type of the surgery is brought by the multidisciplinary teams. Different clinicopathological criteria are taken into consideration: tumor extent, location and patient preference.

Therefore the data concerning the type of surgery do not always follow the radiological findings as the poor shift from mastectomy to breast conservative surgery after NACT is related to the surgeons' attitude for aggressive approach despite the response to NACT (6, 8, 37). Another limitation of the DCE-MRI examination is its relatively low specificity. Concerning the overall performance of DCE-MRI in our study, the false positive rate of 23% after the second cycle and of 15% after the completion of NACT, show that the DCE-MRI may overestimate the residual tumor in responders. The use of the additional MRI techniques like diffusion-weighted imaging, improves the specificity to 80%, according to Fanberget et al. (28), although the use of diffusion-weighted imaging in monitoring treatment response has been limited (37). Another technique is magnetic resonance spectroscopic imaging, which improves the specificity up to 91% (44). Based on the higher cut-off value of 83%, which is the tumor volume reduction suggested by Fangberget et al. (28), the sensitivity remains high—87% after the completion of NACT—with the accuracy of 77% and precision of 73%.

In conclusion, the distinctive target lesion features favoring the response include: the significant size and volume reduction, the TIC flattening, the concentric tumor regression pattern, as early as after the second cycle of NACT. This was the case with the responders in our study, with the tumor volume decrease as the criterion providing the sensitivity of 93% after the completion of the second cycle of NACT. Taking into consideration the role of DCE-MRI in the evaluation of tumor response, our study confirmed high correlation coefficient between the residual tumor size and volume upon the completion of NACT compared to the histopathological size and volume ($P = 0.93$ and $P = 0.89$, respectively), identifying the responders in terms of histologic criteria. The analyzed four parameters in the study confirmed the role of DCE-MRI as an important diagnostic tool for response evaluation. In the subgroup of responders, the mentioned parameters confirmed the validity of the "MRI phenotype" of the candidates for breast conservative surgery, which may be of help to the multidisciplinary teams' therapeutic decisions.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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