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Computer-Aided Evaluation of Breast MRI for the Residual Tumor Extent and Response Monitoring in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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Objective: To evaluate the accuracy of a computer-aided evaluation program (CAE) of breast MRI for the assessment of residual tumor extent and response monitoring in breast cancer patients receiving neoadjuvant chemotherapy.

Materials and Methods: Fifty-seven patients with breast cancers who underwent neoadjuvant chemotherapy before surgery and dynamic contrast enhanced MRI before and after chemotherapy were included as part of this study. For the assessment of residual tumor extent after completion of chemotherapy, the mean tumor diameters measured by radiologists and CAE were compared to those on histopathology using a paired student t-test. Moreover, the agreement between unidimensional (1D) measurement by radiologist and histopathological size or 1D measurement by CAE and histopathological size was assessed using the Bland-Altman method. For chemotherapy monitoring, we evaluated tumor response through the change in the 1D diameter by a radiologist and CAE and three-dimensional (3D) volumetric change by CAE based on Response Evaluation Criteria in Solid Tumors (RECIST). Agreement between the 1D response by the radiologist versus the 1D response by CAE as well as by the 3D response by CAE were evaluated using weighted kappa (k) statistics.

Results: For the assessment of residual tumor extent after chemotherapy, the mean tumor diameter measured by radiologists (2.0 ± 1.7 cm) was significantly smaller than the mean histological diameter (2.6 ± 2.3 cm) ($p = 0.01$), whereas, no significant difference was found between the CAE measurements (mean = 2.2 ± 2.0 cm) and histological diameter ($p = 0.19$). The mean difference between the 1D measurement by the radiologist and histopathology was 0.6 cm (95% confidence interval: −3.0, 4.3), whereas the difference between CAE and histopathology was 0.4 cm (95% confidence interval: −3.9, 4.7). For the monitoring of response to chemotherapy, the 1D measurement by the radiologist and CAE showed a fair agreement ($k = 0.358$), while the 1D measurement by the radiologist and 3D measurement by CAE showed poor agreement ($k = 0.106$).

Conclusion: CAE for breast MRI is sufficiently accurate for the assessment of residual tumor extent in breast cancer patients receiving neoadjuvant chemotherapy. However, for the assessment of response to chemotherapy, the assessment by the radiologist and CAE showed a fair to poor agreement.

Index terms: *Breast neoplasm; Chemotherapy; MR imaging; Computer-aided*

INTRODUCTION

Neoadjuvant chemotherapy has been increasingly used in patients with operable breast cancers as well as those with locally advanced breast cancers. The use of neoadjuvant chemotherapy has allowed formerly unresectable tumors to be resectable and has increased the proportion of breast conservation surgery (1–5). Several studies have shown that the size of residual tumors and the response of a tumor to neoadjuvant chemotherapy are related to the recurrence-free survival rate and thus, a more accurate evaluation of residual tumor extent and response monitoring to chemotherapy have become of paramount importance in clinical practice as well as in research trials (6–10). In 2000, the collaboration between the European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States and National Cancer Institute of Canada Clinical Trials Group suggested the use of Response Evaluation Criteria in Solid Tumors (RECIST) using unidimensional (1D) measurements (11). The use of these criteria has become commonly accepted as the standard in the evaluation of tumor response. However, several limitations of the use of these criteria have been reported and the modification of RECIST has become necessary (12). It has been proposed that the use of three-dimensional (3D) volumetric assessment rather than 1D assessment should be considered (13).

The recent advent of high resolution dynamic contrast-enhanced MRI has provided 3D information of the anatomy and perfusion of breast cancer, thus enabling the extent of the disease to be assessed accurately after chemotherapy (14–20). However, after chemotherapy, MRI often under-estimates or over-estimates the extent of disease due to changes in cellularity or vascularity of tumors (21, 22). Moreover, a volumetric measurement is a particularly labor intensive endeavor that requires much time and effort.

It has been suggested that a computer-aided evaluation program (CAE) of breast MRI using automatic segmentation might be helpful in determining disease extent, but a recent study has shown that CAE of breast MRI was less accurate than a radiologist in the assessment of tumor size in breast cancer patients undergoing neoadjuvant chemotherapy (23). However, the investigation was only a small pilot study that included 15 patients. Controversy remains as to whether CAE is accurate for MRI of breast cancer patients who were treated with neoadjuvant chemotherapy.

Therefore, the purpose of this study was to evaluate the accuracy of CAE in breast MRI for the assessment of residual tumor extent and the monitoring of chemotherapeutic response in breast cancer patients receiving neoadjuvant chemotherapy.

MATERIALS AND METHODS

Patient Population

Our Institutional Review Board approved this study and informed consent was waived for this retrospective analysis. Between December 2006 and April 2008, 76 consecutive patients with breast cancer underwent breast MRI before and after neoadjuvant chemotherapy and curative surgery at our institution. Nineteen patients were excluded due to data loading errors in the application of the CAE. These data loading errors might be explained by the unavailability of the CAE system for the oblique sagittal images. The CAE system used in this study was designed for right-angled sagittal images, so, some images were not loaded according to the scanned angle. Ultimately, 114 MRI examinations of 57 patients were included in the study. Patient characteristics are summarized in Table 1. Mean patient age for this study was 44 years old (range, 24–64). All patients had undergone a core needle biopsy for diagnosis and two separate breast MRI examinations; one examination prior to neoadjuvant chemotherapy and the other examination after completion of chemotherapy and prior to final surgery. The mean interval between completion of chemotherapy and the second MRI examination was 21.1 days (range, 8–51 days). The mean interval between the second MRI examination and surgery was 5.1 days (range, 1–21 days). Forty-seven patients (82%) received taxane plus anthracycline regimens (three cycles for 45 patients and six cycles for two patients), whereas two patients (4%) received an anthracycline-based regimen (three cycles for one patient and four cycles for the other patient). The remaining eight patients (14%) received a trastuzumab plus taxane regimen (six cycles for all patients). The mean durations of the respective neoadjuvant chemotherapies were 49 days for patients who received taxane plus anthracycline, 54 days for patients who received anthracycline, and 112 days for patients who received trastuzumab plus taxane. The mean interval between the 1st and 2nd MRI examination was 80 days (range, 57–99 days) for patients who received three cycles of chemotherapy and 145 days (range, 124–176 days) for six cycles.

MRI Examinations

The MRI protocol was performed with a 1.5 Tesla system (Signa, GE Healthcare, Milwaukee, WI) using a dedicated breast coil (8-channel HD breast array, GE Healthcare, Milwaukee, WI). After an axial localizer image, fat-suppressed T2-weighted fast spin-echo sagittal images were obtained (TR/TE, variable from 5500 to 7150/82; 256 × 160 matrix; field of view: 200 × 200 mm; 1.5-mm slice thickness; no gap). Dynamic contrast-enhanced examinations included one pre-contrast and five post-contrast, bilateral sagittal image acquisitions using a fat-suppressed T1-weighted 3D fast spoiled gradient echo sequence (TR/TE, 6.5/2.5; matrix 256 × 160; flip angle 10°; field of view 200 × 200 mm; 1.5-mm slice thickness; no gap). Gadobenate dimeglumine (0.1 mmol/kg Multihance; Bracco Imaging, Milan, Italy) was injected using an automated injector (Spectris MR, Medrad Europe, Maastricht, The Netherlands) through an indwelling IV catheter. Five post-contrast image series were obtained at 76, 165, 345, 434, and 583 seconds after contrast administration. For all studies, early subtraction (i.e., first postcontrast images minus pre-contrast images), axial reformatted images, and 3D maximum intensity projection images were generated.

Computer-Aided Evaluation Program

For the CAE measurements, an early 1st post-contrast series (obtained at 76 seconds after contrast injection), and four late post-contrast image series (obtained at 165, 345, 434, and 583 seconds after contrast injection) were transferred to a commercially available MR CAE (CADSTREAM™ version 4.1.3, Confirma, Inc., Kirkland, WA) workstation and processed. A color overlay map was placed on all enhancing lesions at the enhancement threshold level in a pixel by pixel comparison across a pre-contrast, early and late post-contrast series. The users could choose a 50% or a 100% enhancement threshold. In this study, we chose the 50% enhancement threshold because, according to several previous studies, the 50% threshold was more sensitive than the 100% threshold in the detection (24, 25) of slowly enhancing lesions frequently found in the neoadjuvant chemotherapy setting.

Delayed phase enhancement type after peak enhancement was classified as persistent, plateau, or washout (26) and appeared as different colors; blue for persistent, yellow for plateau, and red for washout. The CAE automatically segmented and calculated the longest diameter and volume of the all enhancing components (23, 25). Manual segmentation was not available for scattered multiple lesions or lesions with an irregular shape for this CAE system. The same radiologists, who had performed a 1D measurement at a PACS workstation, selected the same lesions for CAE measurement.

Measurement of Tumor Extent

The one-dimensional measurements were performed by two radiologists with eight and three years of experience in the interpretation of breast MRI and retrospectively analyzed pre- and post-chemotherapy MR images in consensus. At the time of tumor measurement, the radiologists were not aware of the histopathology information. A positive lesion was defined as when the signal intensity of the lesion was higher than that of the breast parenchyma, as seen on early subtraction images. The lesion size was measured as the longest diameter of

Table 1. Clinical Characteristics of 57 Study Patients

	No. of Patients (%)
Neoadjuvant chemotherapy regimen	
Anthracycline based	2 (4)
Taxane plus anthracycline	47 (82)
Taxane plus trastuzumab	8 (14)
Pre-chemotherapy clinical stage	
IIB	7 (12)
IIIA	40 (70)
IIIB	4 (7)
IIIC	6 (11)
Post-chemotherapy pathologic stage	
0*	7 (12)
I	6 (11)
IIA	12 (21)
IIB	12 (21)
IIIA	14 (25)
IIIB	0
IIIC	6 (11)
Histological type	
Invasive ductal	56 (98)
Invasive lobular	1 (2)
Surgical method	
Total mastectomy	25 (44)
Partial mastectomy	32 (56)

Note.—*Surgical histology revealed no residual tumor.

the lesion on 21 inch monitors at a picture archiving and communication system (PACS) workstation using electronic calipers. Target lesions included up to a maximum of five lesions per breast, as seen on first post-contrast images. For multiple lesions, the longest diameter of each lesion was separately recorded and the sum of the lesions was calculated. When there was no enhancing lesion seen on first post-contrast images, the lesion size was set to 0 cm.

Assessment of Treatment Response

We evaluated the tumor response for the neoadjuvant chemotherapy according to the three following modalities: 1D measurement by radiologists as well as 1D and 3D measurements by CAE according to the RECIST criteria. For 1D tumor measurements, according to RECIST, the responders group consisted of patients with a complete response (CR) (no enhancing lesion detected on post-chemotherapy MRI) or partial response (PR) ($\geq$ 30% reduction of the sum of maximal diameters) to treatment (11, 27). The non-responders group consisted of patients with stable disease (SD) (< 30% reduction or a < 20% increase of the sum of maximal diameters) or progressive disease (PD) ($\geq$ 20% increase of the sum of maximal diameters).

For 3D volumetric measurements, based on the assumption that the tumor was spherical, PR was defined for tumors with a $\geq$ 65% reduction in the sum of volumes from the baseline level, and SD was defined for tumors with a < 65% reduction or a < 73% increase of the sum of volumes from the baseline level (27). If a tumor had a radius (r), the tumor volume would be calculated as $4/3 \pi r^3$. Therefore, a 30% diameter reduction of the tumor corresponded to the 65% volume reduction, and a 20% diameter increase of the tumor corresponded to the 73% volume increase. PD was defined for tumors with a 73% increase of the sum of volumes or the appearance of a new lesion. Patients were divided into two groups-responders and non-responders-according to RECIST and volumetric measurement, respectively.

Histopathological Analysis

After a partial or total mastectomy, a pathologist evaluated mastectomy specimens with serial 10 mm sections along the longitudinal axis. For the assessment of tumor size, grossly apparent lesions in the sliced tissue were measured and size estimates for smaller lesions obtained microscopically were included. Standardized report templates included the number and sizes of

measurable invasive components as well as the carcinoma in situ components of the tumor. Histopathological tumor diameter was defined as the sum of the longest diameters of all invasive components of the tumor as stated in the histopathology report. The maximum diameter by histopathology was used as a reference standard.

Data and Statistical Analysis

The mean of residual tumor extents after neoadjuvant chemotherapy were compared between the radiologists or CAE and histopathology using the paired Student's t-test. In addition, the agreement between the measurements by the radiologists or the CAE and the histopathological size in the assessment of residual tumor extent after the completion of chemotherapy was assesses by the Bland-Altman plotting method (28). The mean difference between the two measurements and the 95% limits of agreement were calculated. The difference between the two measurements was plotted against the mean of the two measurements. One of the two radiologists reviewed the standardized histopathology report and analyzed the agreement between the measurements.

For the assessment of tumor response, RECIST between 1D measurements performed by radiologists and 1D measurement or 3D volumetric measurements determined by the CAE were compared using weighted kappa (k) statistics between two groups (responders and nonresponders). The rates of concordance and discordance for the assessment were analyzed. Statistical analyses were carried out using SPSS for Windows 12.0 (SPSS, Chicago, IL) and MedCalc for Windows, version 9.3.1 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Assessment of Residual Tumor Extent

The mean number of measured lesions per breast was 1.9 ± 1.3 (standard deviation) (range, 1–5). After chemotherapy, the mean tumor diameter measured by radiologists and CAE was 2.0 ± 1.7 cm (mean ± standard deviation) (range, 0–9.0 cm) and 2.2 ± 2.0 cm (range, 0–9.6 cm) respectively, and 2.6 ± 2.3 cm (range, 0–9.2 cm) based on the histopathological assessment. A statistically significant difference was found between radiologists' measurements and histological diameters (p = 0.01), however, no significant difference was found between the CAE measurements and histological diameters (p = 0.19).

Figure 1 shows the plots that propose the differences between measurements by the radiologists or CAE and histopathology, relative to the mean of the two measurements. The mean difference between the histopathological and radiologists' measured diameters was 0.6 cm with 95% limits of agreement from −3.0 to 4.3. The mean difference between histopathological and CAE assessed diameters was 0.4 cm with 95% limits of agreement from −3.9 to 4.7. All of the two plots showed good agreement between each method.

Assessment of Response to Chemotherapy

The mean tumor diameter reduction was 40 ± 29.2% as determined by the radiologists (5.3 ± 2.7 cm before chemotherapy and 2.0 ± 1.7 cm after chemotherapy) and 43 ± 34.0% by CAE (5.6 ± 3.6 cm before chemotherapy and 2.2 ± 2.0 cm after chemotherapy). The mean tumor volume reduction was 85 ± 23.4% as determined by the CAE (17.0 ± 21.2 cc before chemotherapy and 1.5 ± 2.5 cc after chemotherapy).

According to the 1D measurement by the radiologists, 47 patients (83%) were responders (10 patients with CR and 37 patients with PR) and 10 patients (18%) were non-

Table 2. Comparison of Responsiveness between 1D Measurements by Radiologist and CAE

		Radiologist (1D)				Total
		CR	PR	SD	PD	
CAE (1D)	CR	8	3	0	0	11 (19%)
	PR	2	28	5	0	35 (61%)
	SD	0	6	5	0	11 (19%)
	PD	0	0	0	0	0 (0%)
	Total	10 (18%)	37 (65%)	10 (18%)	0 (0%)	57 (100%)

Note.— Patients were divided into two groups as responders and non-responders. Complete response (CR) and partial response (PR) were defined as responder group, whereas stable disease (SD) and progressive disease (PD) were defined as non-responder group. Weighted kappa value (k) between radiologist and computer-aided evaluation program for two groups of responsiveness was 0.358. 1D = unidimensional, CAE = computer-aided evaluation program
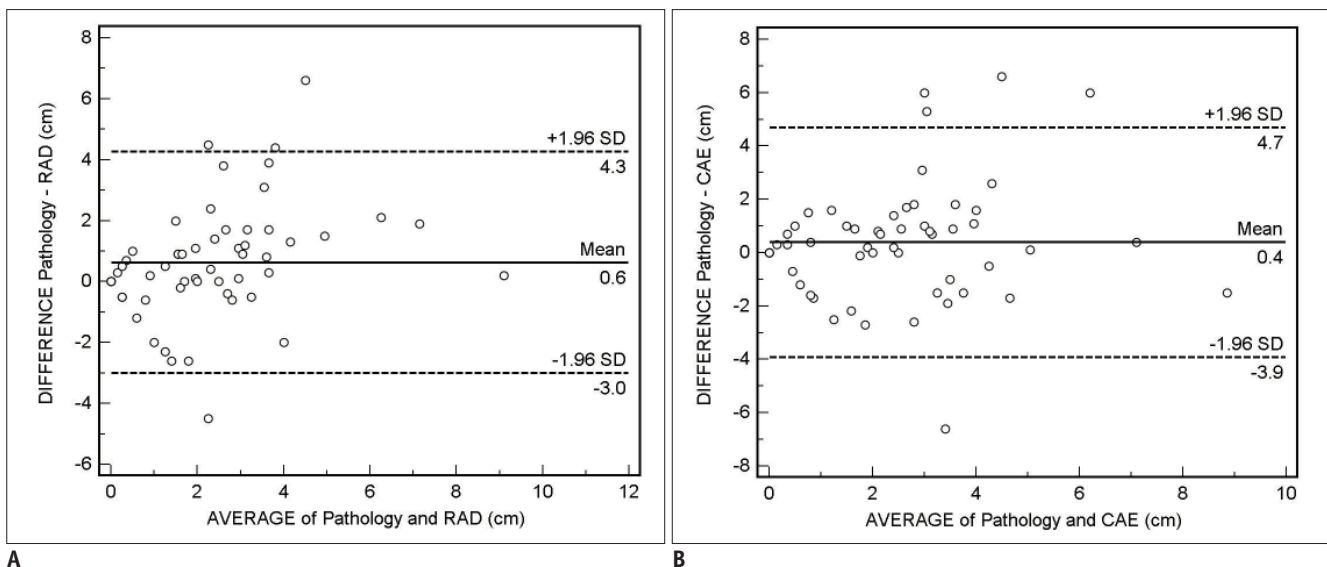

Fig. 1. Bland-Altman plots of manual measurements by radiologists (RAD), computer-assisted evaluation program (CAE), and histopathologic unidimensional measurements of residual tumor extent after neoadjuvant chemotherapy.
Solid line (center) represents mean of differences. Top dashed line represents upper limit of agreement (mean difference plus two times standard deviation); bottom line represents lower limit of agreement (mean difference minus two times standard deviation).
A is for agreement between RAD and histopathology (mean difference = 0.6 cm, 95% limits of agreement: −3.0 to 4.3 cm) and **B** is for agreement between CAE and histopathology (mean difference = 0.4 cm, 95% limits of agreement: −3.9 to 4.7 cm).

responders (10 patients with SD and no patients with PD) (Tables 2, 3). According to the 1D measurement by CAE, 46 patients (81%) were responders (11 patients with CR and 35 patients with PR) and 11 patients (19%) were non-responders (11 patients with SD and no patients with PD) (Table 2). According to the 3D volumetry, 50 patients (88%)

Table 3. Comparison of Responsiveness between Unidimensional (1D) Measurements by Radiologist and Volumetric (3D) Measurements by CAE

		Radiologist (1D)				Total
		CR	PR	SD	PD	
CAE (3D)	CR	9	3	0	0	12 (21%)
	PR	1	29	8	0	38 (67%)
	SD	0	5	2	0	7 (12%)
	PD	0	0	0	0	0 (0%)
	Total	10 (18%)	37 (65%)	10 (18%)	0 (0%)	57 (100%)

Note.— Patients were divided into two groups as responders and non-responders (similar to Table 3). Weighted kappa value (*k*) between 1D measurement by radiologist and 3D measurement by CAE for two groups of responsiveness was 0.106.
1D = unidimensional, 3D = three dimensional, CAE = computer-aided evaluation program, CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease
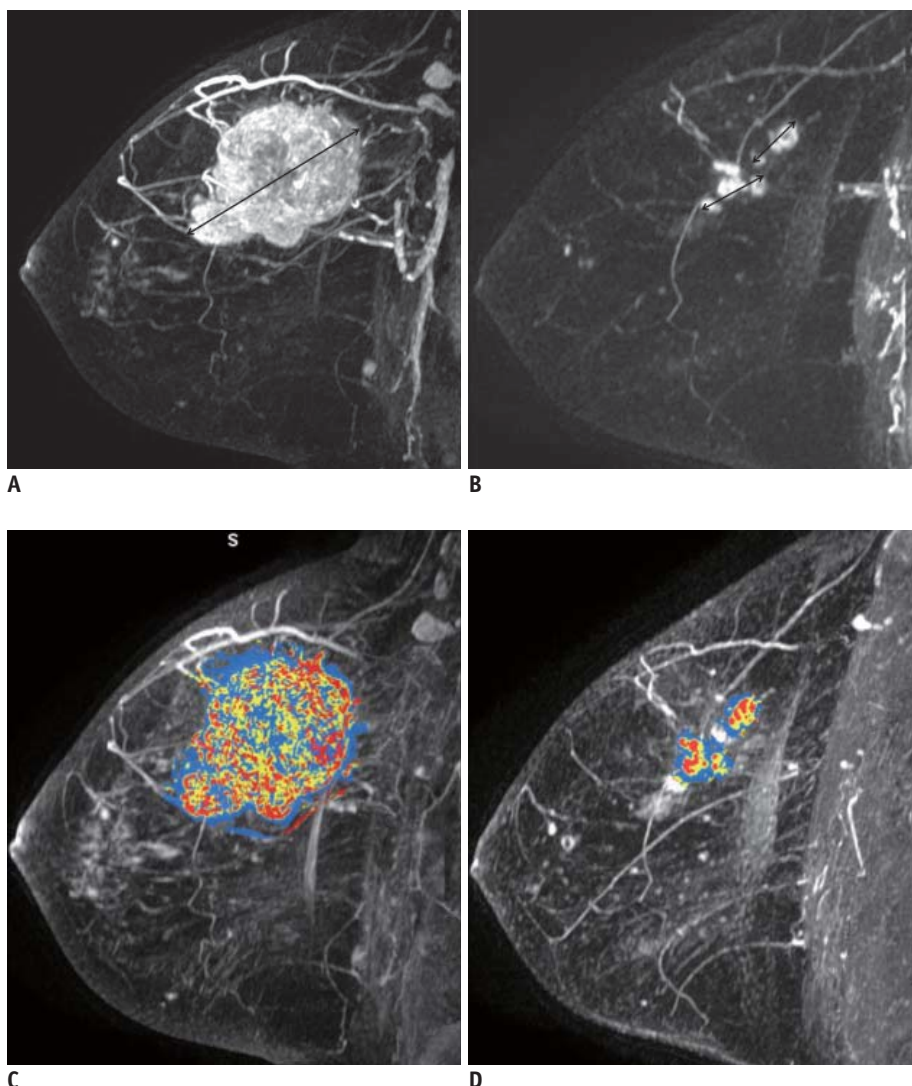

A

B

Fig. 2. Concordant case between unidimensional and three dimensional measurements is presented.
Imaging measurements are presented for 52-year-old woman diagnosed with infiltrating duct carcinoma upon initial examination (indicator in **A**) and follow-up examination (indicators in **B**). After chemotherapy, 1D measurement shows 57% diameter reduction from 6.7 cm (**A**) to 2.9 cm (**B**). According to RECIST, this tumor is categorized as responder. Computer-aided volumetry shows 94% volume reduction from 61.8 cc (**C**) to 3.5 cc (**D**). According to volumetric criteria; this tumor is also categorized as responder.

C

D

were responders (12 patients with CR and 38 patients with PR) and seven patients (12%) were non-responders (seven patients with SD and no patients with PD) (Table 3). The 1D measurements by the radiologists and by CAE were concordant in 46 (81%) and discordant in 11 (19%) of the 57 patients, resulting in a weighted kappa value of 0.358, which indicated a fair agreement between the two methods. The 1D measurement by the radiologists and 3D measurements by CAE were concordant (Fig. 2) in 44 (77%) and discordant (Fig. 3) in 13 (23%) of the 57 patients, resulting in a weighted kappa value of 0.106, which indicated a poor agreement between the two methods. Eight patients were non-responders according to the 1D measurements, but were responders by 3D volumetry. Five patients were non-responders by 3D volumetry, but were responders by 1D measurement by radiologist (Table 3).

DISCUSSION

This study evaluated the accuracy of CAE in breast MRI for the assessment of residual tumor extent and the monitoring of response after neoadjuvant chemotherapy. According to our results for the assessment of residual tumor extent in breast cancer patients receiving neoadjuvant chemotherapy, the mean difference between 1D measurement by the radiologists and the histopathological assessment was 0.6 cm, whereas the difference between the CAE measurements and the histopathological assessment was 0.4 cm. The 95% confidence interval for the measured difference between the radiologists and histopathological assessment was in the range from −3.0 to 4.3 cm (93%, 53 of 57), whereas the difference between the measurement by CAE and the histopathological assessment was in the range of −3.9 to 4.7 cm (91%, 52 of 57). The measurement by radiologists
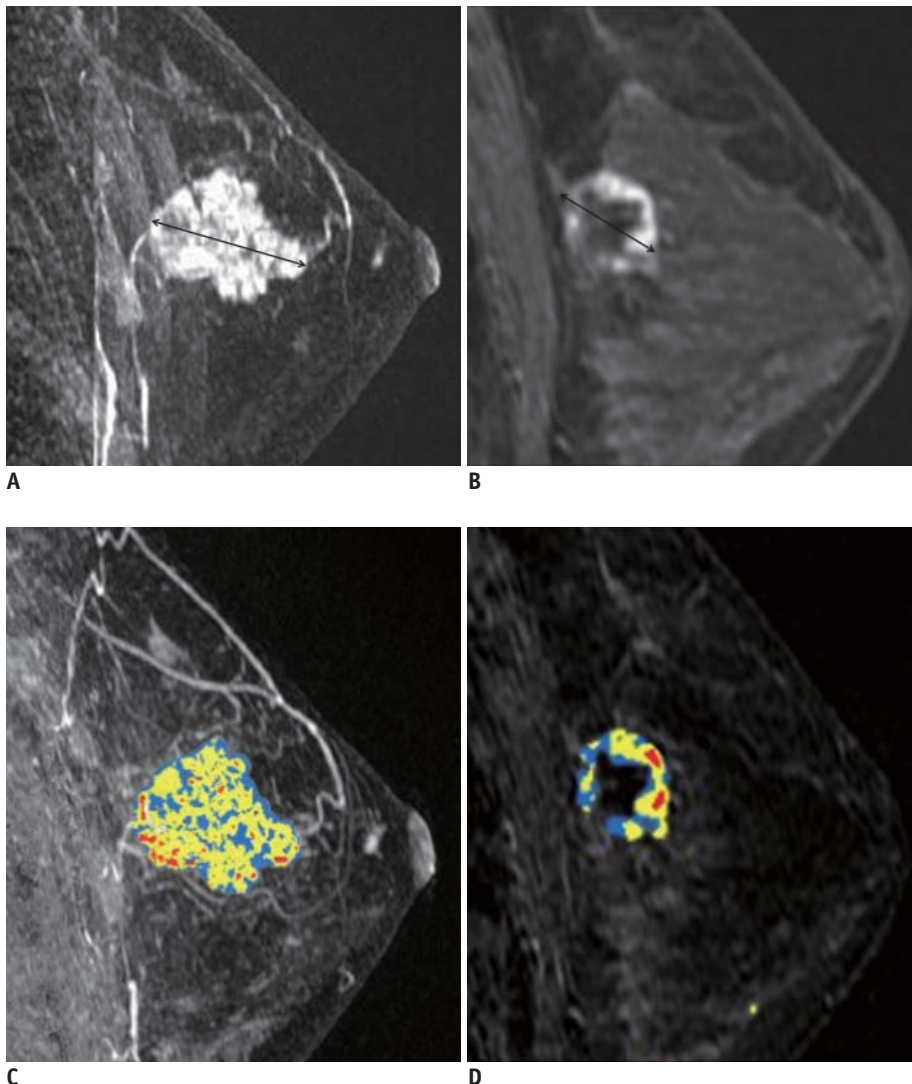

Fig. 3. Discordant case between unidimensional and three dimensional measurements is presented.
Imaging measurements are presented for 36-year-old woman diagnosed with infiltrating duct carcinoma upon initial examination (indicator in **A**) and follow-up examination (indicator in **B**). After chemotherapy, 1D measurement shows 21% diameter reduction from 5.3 cm (**A**) to 4.2 cm (**B**). According to RECIST, this tumor is categorized as non-responder. Computer-aided volumetry shows 90% volume reduction from 6.4 cc (**C**) to 0.64 cc (**D**). According to volumetric criteria, this tumor is categorized as responder.

underestimated the 1D measurement compared to the histological tumor diameter ($p = 0.01$); however, no difference was found between the CAE measurements and the histological diameter ($p = 0.19$). These results indicate that the measurement of CAE is more accurate than the measurement by radiologists and can be used in place of direct measurement by a radiologist.

As the underestimation of residual tumor extent after neoadjuvant chemotherapy can lead to early local relapse or a repeated excision that hampers conservation surgery and overestimation of residual tumor extent can lead to overtreatment in breast cancer patients, the accurate assessment of lesion extent is crucial. A previous study evaluating the use of breast MRI in patients with breast cancer following chemotherapy reported a false negative rate of 31% (4 of 13) and underestimated cases (15%, 2 of 13) (21), which was consistent with the results of our study where the measurement by radiologists underestimated the 1D measurement compared with the histological tumor diameter ($p = 0.01$). Such underestimation on MRI might be explained by reduced contrast enhancement and flattening of the washout time-signal intensity curve due to an antiangiogenic effect of cytotoxic chemotherapy (21, 29). Therefore, lesion size measurement on delayed phase images of dynamic contrast enhanced MRI would be more accurate than those on early phase images used in our study.

The use of RECIST, which measures the longest diameter of a tumor, has been accepted to be as accurate as bidimensional measurements according to the WHO criteria. However, many limitations have been reported for the use of RECIST and the necessity of modification for volumetric or functional assessment has been raised (12, 13). Volumetric measurements were expected to provide a more precise quantification of tumor burden and to be less affected by inter-observer variability, especially for multiple, irregular, scattered or confluent lesions after chemotherapy. Moreover, several investigators have found that 3D volumetry correlated with prognosis (30, 31). In one study, Partridge et al. (30) found that the initial tumor volume and final change in MRI volume in breast cancer patients undergoing neoadjuvant chemotherapy were significant independent predictors of recurrence free survival based on the use of multivariate analysis. In another study, Hylton et al. (31) reported that MRI volume change after one cycle of chemotherapy showed the strongest correlation for the prediction of end-of-treatment response.

Even with these promising results, 3D volumetry has

been considered laborious in clinical practice and has been under-established to determine treatment response (13). In our study, a commercially available CAE provided simple measurements with automatic segmentation of irregular masses that allowed the use of the program to be acceptable for a clinical setting. However, in the monitoring of response to chemotherapy, the 3D volumetric response determination by CAE did not show good agreement with the 1D response category ($k = 0.106$), although the 1D measurements by the radiologists and by CAE showed a fair agreement ($k = 0.358$). This might be due to the use of a 65% volume reduction criterion. Of the lesions assessed, 23% (13 of 57) were discordant and a larger reduction in tumor size was required for the categorization of responders on 1D measurement. This condition may have resulted due to the fact that the present criteria were based on the assumption that tumors were spherical and that responding patients have equivalent percentage reductions in the measurements of length, width, and depth of tumors. Therefore, when a tumor had an irregular shape or was diffusely scattered for distribution, discrepancy of the assumption of spherical tumor and measured tumor tended to increase and 1D measurement of residual tumors tended to be overestimated than real tumor volume because the 1D measurement was determined by the maximum diameter. Similarly, in a previous study involving the comparison of 1D and 2D measurements, simulation models with increasing irregularities increased the discordance rates of PR and SD categories between the two methods (13). If the comparison would have been between 1D and 3D measurements in the simulation model, it could be expected that even a small difference may have lead to a larger difference in triplicated calculations, hence leading to a different treatment decision.

This study had some limitations; this was a retrospective study with a small sample size and was conducted at a single institute. In addition, it was not possible to correlate computer-aided volumetric results with tumor volumes determined by histopathology, as the 3D volumetric results were not available in the clinical situation. Third, there were 19 cases (25%, 19 of 76) of data loading errors in the application of the CAE program. Thus, we cannot generalize our results for the evaluation of all ranges of breast MRI in the neoadjuvant chemotherapy setting. Sagittal breast MRI scanning at a right angle might be considered for the possible solution. Fourth, the time interval between the completion of chemotherapy and 2nd (preoperative) MRI

was variable (21.1 days: range, 8–51 days), which could have affected results. However, there is no established recommendation for the adequate timing of preoperative MRI after neoadjuvant chemotherapy. This question is beyond scope of this study.

In conclusion, CAE for breast MRI is sufficiently accurate for the assessment of residual tumor extent in breast cancer patients receiving neoadjuvant chemotherapy. However, for the assessment of response to chemotherapy, the radiologists' assessment and CAE assessment showed fair to poor agreements.

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