Impact of parametric imaging on contrast-enhanced ultrasound of breast cancer

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Abstract

Purpose To prospectively evaluate the usefulness of contrast-enhanced ultrasound (CEUS) using parametric imaging for breast cancer in a multicenter study.

Methods A total of 65 patients with breast cancer were included in this study. CEUS was performed, and still images on peak time (S), accumulated images (A) and parametric images (P) were generated from the raw data. Four blind reviewers ranked the best visible images as first place, and determined second and third place consecutively. We compared the average ranking of each image. The maximal diameter of the tumor determined on ultrasonography and MRI was compared with the corresponding pathological maximal diameter for 48 of the 65 patients. The correlation between the diameter determined by two experts and two beginners was analyzed.

Results The average rank of visibility was as follows: P, 1.44; A, 2.04; and S, 2.52. The correlation between each image and the pathology was as follows: P, r=0.664; A, r=0.630; S, r=0.717; and MRI, r=0.936. There were no significant differences among the correlation between the experts and beginners in each image.

Conclusions The use of parametric imaging improves the visibility of CEUS. The maximal diameter of the tumor determined on CEUS correlates substantially with the pathology.

Keywords: contrast-enhanced ultrasound, Sonazoid, parametric image, breast cancer, visibility

Introduction

Contrast-enhanced ultrasound (CEUS) makes it possible to assess the detailed hemodynamics of breast lesions in real time. Previous studies have reported that CEUS is useful for differentiating between benign and malignant breast lesions [1, 2], evaluating the disease extent [3, 4], and assessing the tumor response after neoadjuvant chemotherapy [5, 6].

However, CEUS with Sonazoid is performed using harmonic imaging under moderate acoustic power (mechanical index set to approximately 0.2). As a result, the signal from the echogenic tissue surrounding breast cancers cannot be sufficiently suppressed, and the visibility of the enhancing effect decreases. Therefore, careful observation with moving enhancement images and adequate experiments are required to assess the accurate area of the tumor. In addition, since this examination is subjective, it is sometimes difficult to obtain agreement among operators.

Parametric imaging, in general, is images reconstructed by focusing on one parameter in the image diagnosis. In MRI lesions, it has been reported that parametric imaging can be used to assess the tumor response after neoadjuvant chemotherapy [7]. It has also been utilized as an analysis tool on CEUS. It enables color display reflecting real-time changes in hemodynamics. In hepatic lesions, it has been reported that parametric images may be used to obtain detailed hemodynamic information of the hepatic parenchyma and make a diagnosis of hepatic disease [8-11]. In breast lesions, previous studies suggest that parametric imaging is useful for differentiating between malignant and benign breast tumors [12, 13]. Although it has been incorporated into ultrasound systems as a standard analysis software program, parametric imaging remains underutilized.

Parametric imaging makes it easy to distinguish the lesions of breast cancer visualized in the early phase from the breast parenchyma. If the visibility of CEUS is improved by parametric imaging, then the images will become more objective, which may reduce the differences between ultrasonographic experts and beginners. Consequently, it is important for assessing the location and extent of breast cancer. Recently, MRI of the breast has been reported to be the most accurate modality for assessing the extent of breast cancer [14, 15]. However, patients undergo MRI in the prone position. In contrast, when performing CEUS, the patient is in the supine position, the same position as during surgery. Therefore, the operator can accurately assess the extent of breast cancer and determine a safe surgical margin.

In this study, we prospectively examined the impact of parametric imaging on CEUS of breast cancer in a multicenter study.

Materials and methods

Patients

A total of 66 patients with breast cancer (59 patients at Mie University Hospital and 7 patients at Nara Medical University Hospital) who underwent surgery between April 2014 and March 2015 were enrolled in this study. One patient was excluded because no residual tumor cells were found in the pathological specimen of mastectomy after a surgical biopsy. Hence, a total of 65 patients (76 image sets) were included in this study. Five patients (16 image sets) who received neoadjuvant chemotherapy were included. These subjects underwent CEUS several times; therefore, five patients were considered as 16 image sets in total.

The median age of the patients in this study was 63 years (range 26 - 87 years). The pathological analysis revealed 12 noninvasive carcinomas (11 ductal carcinomas *in situ* (DCIS) and 1 lobular carcinoma *in situ*), 53 invasive carcinomas (43 invasive ductal carcinomas, 5 invasive lobular carcinomas, 4 mucinous carcinomas, and 1 invasive micropapillary carcinoma).

Contrast-enhanced US

CEUS was performed on the day before surgery in all patients except those who received neoadjuvant chemotherapy. The LOGIQ S8 (GE Healthcare Japan) ultrasound system with the 11L probe (amplitude modulation general) was used. The LOGIQ S8 and following image analysis software package were lent for free. The mechanical index was set to 0.18-0.22. The focus was set at the bottom of the tumor.

Sonazoid (perfluorobutane, 0.01 ml/kg; Daiichi Sankyo, Japan) was administered into the antebrachial vein followed by a 10-ml flush of normal saline. The probe was held at one cross-section.

Early enhanced images obtained from before injection to 50 seconds after the injection of Sonazoid were saved as raw data on the system's hard disk drive. A time intensity curve was drawn by locating a region of interest (ROI) on the tumor with the saved movie data using the software program built into the system. Subsequently, still images on peak time and accumulated images were generated. The peak time was defined as the point at which the maximum contrast intensity was obtained. Accumulated images were generated from the time at which the tumor became enhanced up to 5-14 seconds, including the peak time.

Parametric Images

Parametric imaging was performed using the proprietary image analysis software package incorporated into the LOGIQ S8. The parameter was the arrival time.

The system set the point at which the contrast agent reached the lesion as time zero and sequentially calculated the arrival time at individual pixels. There are many reports that have utilized a color map gradation [10, 12, 13]. In a similar manner, we colored the map from red to purple per second.

MRI

MRI was performed on a 1.5-T system (Signa HDxt, GE Healthcare). All patients underwent MRI in the prone position using parallel imaging with a dedicated breast coil. After obtaining bilateral T1-weighted images, fat-suppressed T2-weighted images, diffusion images, and dynamic contrast-enhanced images were obtained.

The breast was imaged before and at 60 seconds, 120 seconds, and 5 minutes after a bolus injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist, Schering) on axial plane imaging. Coronal and sagittal sequences were also acquired. Then, the maximal tumor diameter was measured in the same dimension as ultrasonographic imaging.

Pathology

All surgical specimens were processed by pathologists according to the general rules for the clinical and pathological recording of breast cancer, edited by the Japanese Breast Cancer Society. The specimen with the maximum diameter was captured on a computer using a virtual slide system (VS100, Olympus), followed by measurement of the diameter.

Assessment of Visibility

Visibility is the degree of being easy to distinguish the lesions of breast cancer visually. All ultrasonographic images were independently evaluated by four blind reviewers: one expert and one beginner in breast ultrasonography at each institution. Two reviewers at Nara Medical University Hospital reviewed the images obtained at Mie University Hospital, and two reviewers at Mie University Hospital reviewed the images obtained at Nara Medical University Hospital. All patient information was blinded to the image reviewers.

The reviewers assessed the visibility of the parametric images, still images on peak time, and accumulated images, and ranked the best visible images as first place, second-best visible images as second place, and the worst visible images as third place. We then compared the average ranking of each image.

Differences in the Tumor Size between the Images and Pathology

The reviewers measured the maximal diameter of the lesion considered to reflect the extent of the tumor on three types of ultrasonographic images. The maximal diameter determined on ultrasonography and MRI was compared with the corresponding pathological maximal diameter in the surgical specimens.

In this analysis, out of 65 patients, four patients were excluded due to a lack of MRI data, five patients receiving neoadjuvant chemotherapy were excluded, three patients were excluded because diffuse enhancement of the entire breast parenchyma over the probe width obscured the identification of the exact tumor area, and five patients were excluded because the pathological section was different from the ultrasonographic section. Therefore, a total of 48 patients (6 DCIS, 42 invasive carcinomas; 35 invasive ductal carcinomas, 3 invasive lobular carcinomas, and 4 mucinous carcinomas) were included in this analysis.

Comparison between the Experts and Beginners

The correlation between the tumor diameter determined by an expert and a beginner using the three types of ultrasonographic images was analyzed. Since the number of cases examined at Nara Medical University Hospital was only three, 45 cases analyzed at Mie University Hospital were included in this analysis.

Statistical Analysis

The computer program IBM® SPSS® statistics for Mac Ver. 22 was used for the statistical analysis. The Friedman test was performed to assess the visibility ranking. The correlation between each image and the pathology was evaluated according to the interclass correlation coefficient. The degree of the correlation coefficient was considered as follows: 0.01 to 0.20 as “slight,” 0.21 to 0.40 as “fair,” 0.41 to 0.60 as “moderate,” 0.61 to 0.80 as “substantial,” 0.81 to 0.99 as “almost perfect,” and 1.00 as “perfect” [16]. P values of less than 0.05 were considered to be significant.

Results

Assessment of Visibility

The average rank of the parametric images, still images on peak time, and accumulated images was as follows: parametric images, 1.44; accumulated images, 2.04; and still images on peak time, 2.52. The parametric images were statistically ranked the highest (Figure 1). Figure 2 shows representative cases: invasive ductal carcinoma (Figure 2A), ductal carcinoma *in situ* (Figure 2B), invasive lobular carcinoma (Figure 2C), and mucinous carcinoma (Figure 2D).

The experts statistically considered the parametric images to be the most visible images (Table 1a). The beginners also considered the parametric images to be the most visible; however, there were no significant differences between the parametric images and accumulated images (Table 1b).

Difference in the Tumor Size between the Images and Pathology

The median tumor diameter assessed in the surgical specimens was 2.44 cm (range 0.29-4.09 cm). The correlation between the parametric images and pathology was substantial (r=0.664). The size determined on accumulated images (r=0.630) and the still images on peak time (r=0.717) was also substantially correlated with the pathology. MRI showed a higher correlation with the pathology than the three ultrasonographic images (r=0.915) (Table 2, Figure 3).

The difference between the parametric images and pathology was 0.69 cm on average. This result demonstrated that the parametric images tended to overestimate the tumor size. A total of 16 cases were overestimated by more than 1 cm on the parametric images. Four of five DCIS cases were overestimated by more than 1 cm. Only one case, involving invasive lobular carcinoma, was underestimated by more than 1 cm.

Comparison between the Experts and Beginners

The correlation between the tumor diameter determined by the experts and beginners using the three ultrasonographic images was as follows: parametric images, 0.873; accumulated images, 0.807; and still images on peak time, 0.880 (Table 3). There were no significant differences between the parametric images and conventional analysis images.

Discussion

CEUS of the breast, which can be used to visualize detailed tumor vessels, is expected to be a new modality with the ability to differentiate between benign and malignant breast lesions, evaluate the disease extent, and assess the tumor response after neoadjuvant chemotherapy [17]. For breast surgeons in particular, it is very important that CEUS enables an assessment of the extent of breast cancer in the operative position. Since assessments of the extent with MRI are conducted in the prone position, CEUS can supplement the information obtained in the supine position. Additionally, a previous study showed that CEUS was a more reliable method for obtaining an accurate assessment of the breast tumor size than gray-scale ultrasound [3]. This indicates that CEUS is useful for determining the appropriate surgical margin.

However, CEUS is still not yet generally performed, being performed at only a few hospitals in Japan. We speculate that it is difficult to assess the enhanced area accurately, which prevents the use of CEUS from becoming widespread. CEUS can be applied to visualize neovascularization within and around the tumor and can potentially be used for tumor boundary identification and lesion characterization [3]. However, on still images on peak time and accumulated images, the degree of enhancement of the tumor is represented monochromatically. Therefore, there is a tendency for operators to be unable to distinguish the enhancement of malignant lesions from that of the breast parenchyma and therefore assess the tumor extent, especially on still images alone.

In this study, we used parametric images, capable of capturing real-time changes in hemodynamics on still images, in addition to still images on peak time and accumulated images, which are existing tools for analyzing CEUS images. Parametric images can be used to detect tumor vessels enhanced in the early phase and visualize and distinguish the tumor extent clearly from the breast parenchyma based on coloring of the tumor tissue mainly from red to orange. Consequently, we suspect that parametric imaging improves the visibility of CEUS.

As a result of the assessment by blind reviewers, we observed that parametric images have better visibility than still images on peak time and accumulated images. In the current study, the beginners considered the visibility of accumulated images to be equivalent to that of parametric images. This result suggests that, because of their inexperience with accumulated images, beginners are impressed that accumulated images have superior visibility to that of gray-scale ultrasonographic images and still images on peak time, which they are used to seeing.

Yuan Z et al. [13] reported that parametric images enable the objective distinction of malignant and benign breast tumors, clarifying the degree of homogeneity or heterogeneity within the tumor. Although the assessment of CEUS images tends to be subjective, owing to improvements in the visibility with parametric imaging, the images may be more objective not only in the differentiation between benign and malignant but also in the assessment of the tumor extent and the tumor response after neoadjuvant chemotherapy. If the impression that CEUS is difficult to assess is removed by parametric imaging, then the opportunities for CEUS to be actively performed will increase.

In the comparison between the tumor extent assessed with CEUS and pathology, there was a substantial correlation; the correlation coefficient between the parametric images and pathology was 0.664, while that between still images on peak time and pathology was 0.717, and that between the accumulated images and pathology was 0.630. There were no significant differences among the three types of ultrasonographic images. This result indicates that even existing methods of analyzing CEUS can be used to express the accurate extent of the tumor sufficiently.

Unfortunately, each CEUS image was inferior to the corresponding MRI image in terms of the correlation with the pathology. MRI has been recognized as being the most accurate method for assessing tumor size [15]. In this study, MRI also showed a high correlation to the pathology. One advantage of CEUS is that we can assess the extent of breast cancer in the operative position and thus determine the appropriate surgical margin. The result that only one case was underestimated by more than 1 cm on the parametric images is also important to excise the tumor completely. Compared with MRI, CEUS can be performed more easily and inexpensively, within a shorter period of time, and in the same position as that used during surgery. We expect this modality to be a method with a high utility.

One reason that the parametric images were inferior to the corresponding MRI images in terms of the correlation with the pathology is the high rate of overestimated tumor extent. The tumors that were enhanced slightly and slowly, such as DCIS, exhibited a slight contrast with the breast parenchyma and tended to be assessed with a low accuracy. Additionally, in the cases in which the brightness of the breast parenchyma was high, the parametric image system colored the parenchyma the same as the enhanced lesions. Thus, the operator may misread the parenchyma as part of the tumor and overestimate the tumor extent. Technical improvements to control the appropriate brightness of the breast parenchyma are required in the future. Then both the visibility and accuracy of the assessment of tumor extent will be improved, and CEUS will become a more worthwhile modality.

There are some limitations associated with this study: (1) the number of patients was small; (2) there was variation in the pathological characteristics; (3) we did not assess moving images (all images prepared for this study were still images, and there is a possibility that moving images show a higher correlation with the pathology in terms of the tumor size); (4) the only parameter of color mapping was the arrival time, and other parameters, such as the peak intensity as reported by Zhao et al. [12], should be considered; and (5) the reviewers assessed each image in the same sequence: still images on peak time, accumulated images, and parametric images. This may have caused the lack of large differences noted between the types of ultrasonographic images.

Conclusion

Our results indicated that using parametric imaging improved the visibility of CEUS in comparison with still images on peak time and accumulated images. Additionally, the CEUS images substantially correlated with the pathology, although they were inferior to MRI. We hope that parametric imaging, considered to be clearly visible by both experts and beginners, will be incorporated into ultrasound systems as a standard analysis software program, providing a breakthrough for the widespread use of CEUS.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Ethical Standards

This study was performed at Mie University Hospital and Nara Medical University Hospital. The study was approved by the Ethical Review Board of both hospitals (UMIN000013345). Written informed consent was obtained from all patients.

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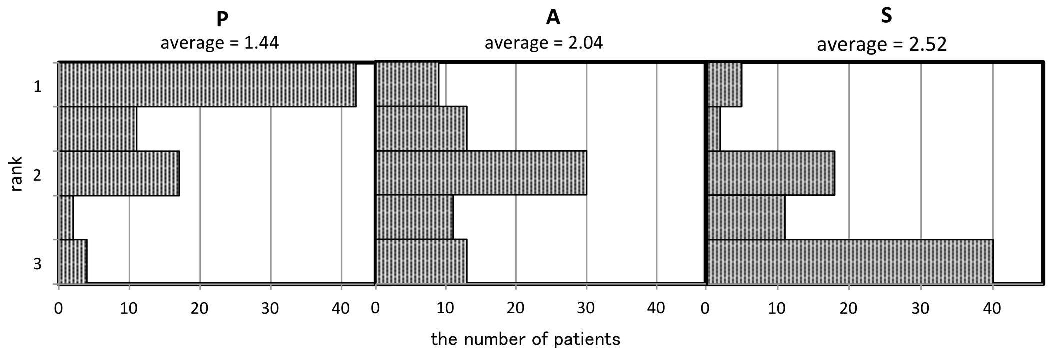
Figure legends

Fig. 1 The average rank of the parametric images, still images on peak time, and accumulated images. The parametric images were statistically ranked the highest.

Fig. 2 Representative images. **A.** Invasive ductal carcinoma, **B.** Ductal carcinoma *in situ*, **C.** Invasive lobular carcinoma, **D.** Mucinous carcinoma.
a. Grey-scale image; **b.** Still image on peak time; **c.** Accumulated image; **d.** Parametric image; **e.** Pathology of the surgical specimen.

Fig. 3 The correlation between each image and the pathology.



	p value
P - S	< 0.001 *
P - A	0.001 *
S - A	0.022 *

* : Statistically significant
P : Parametric images
A : Accumulated images
S : Still images on peak time

Figure 1

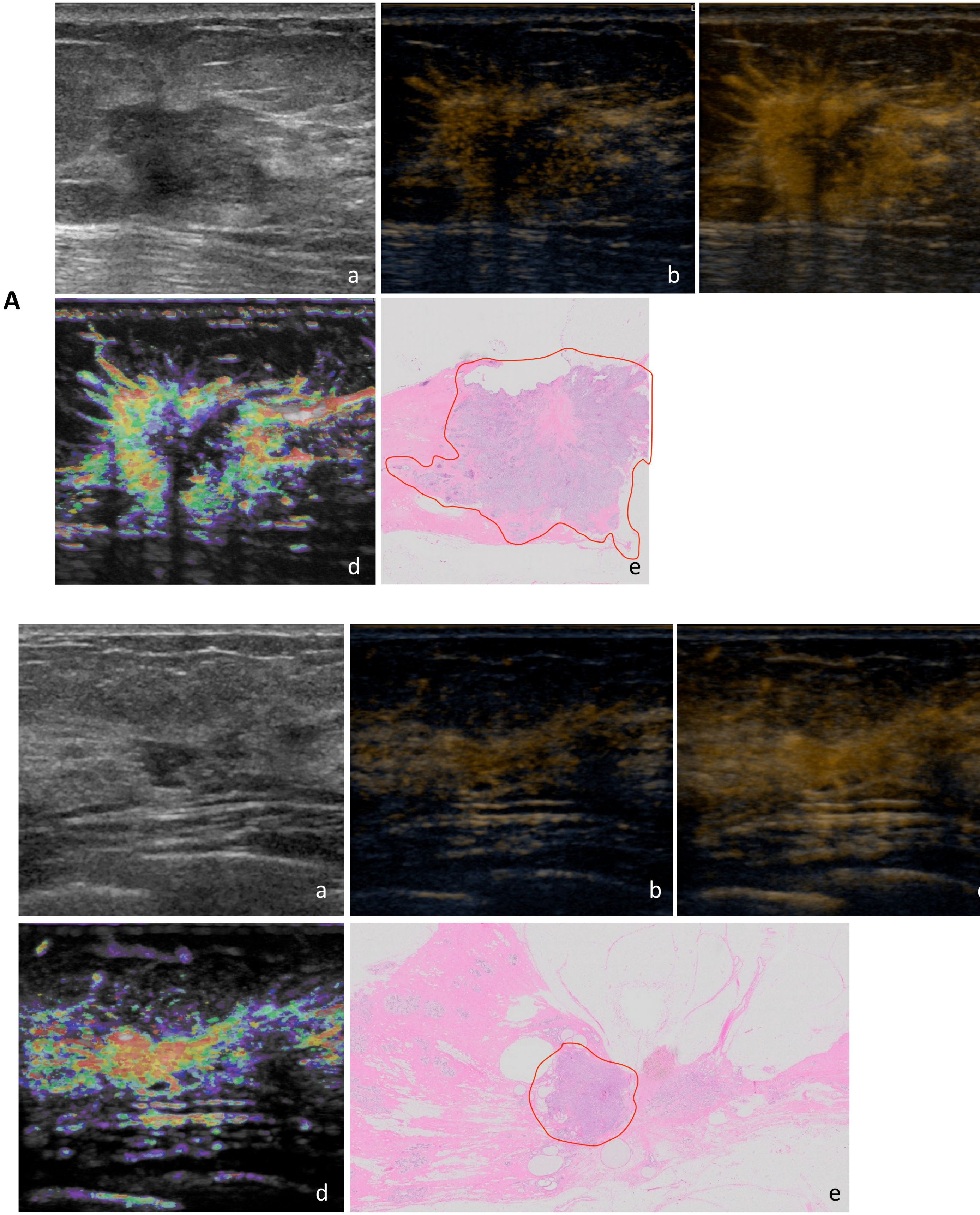


Figure 2

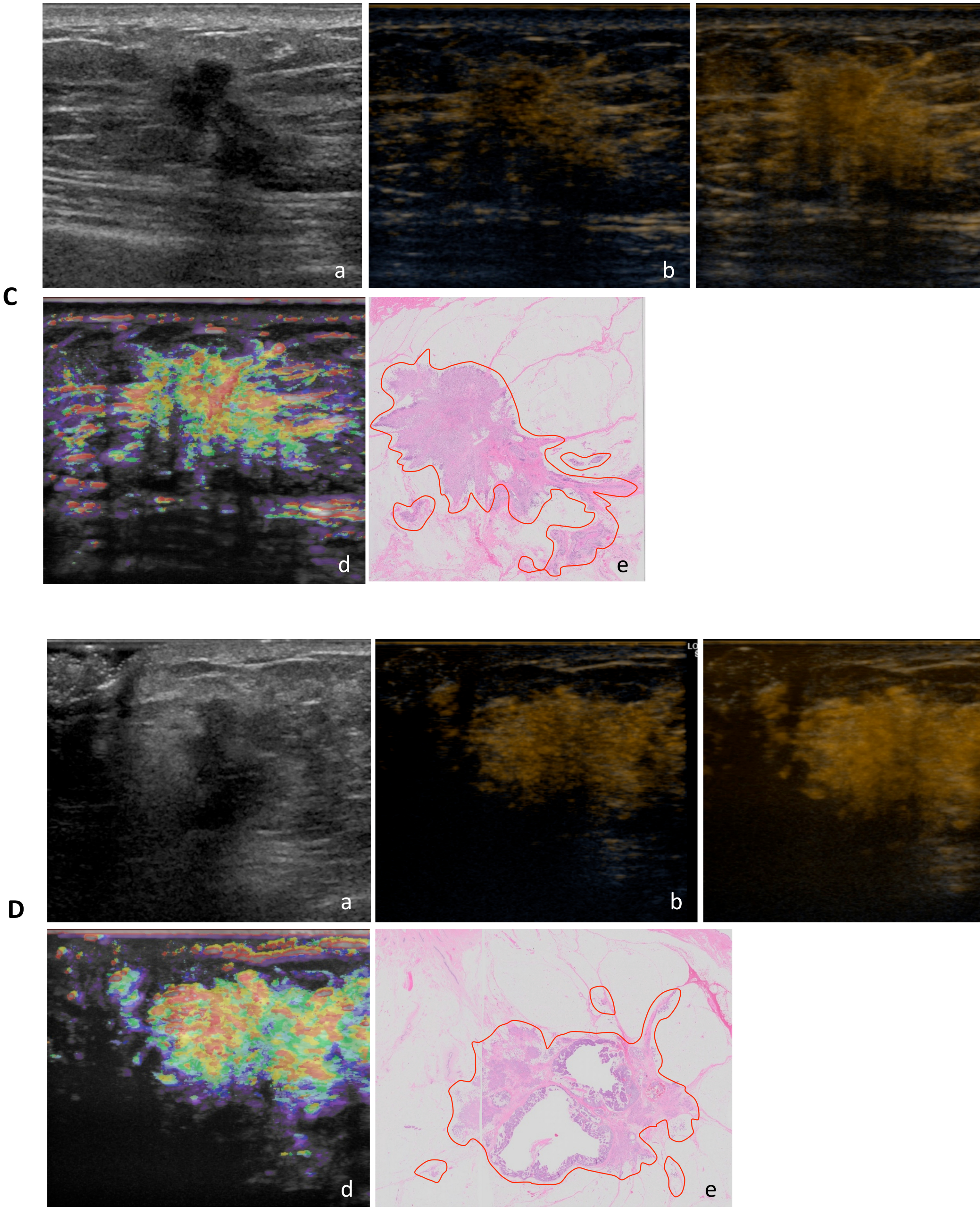


Figure 2

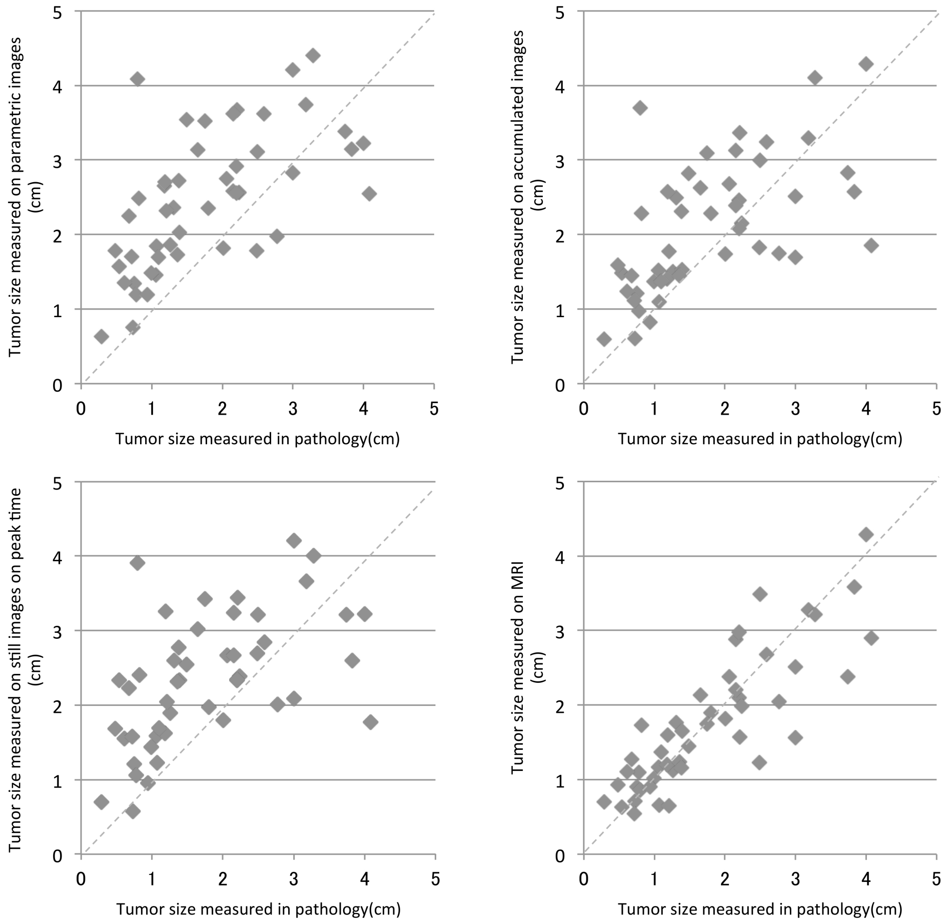

Tumor size measured on parametric images (cm)
Tumor size measured in pathology(cm)
Tumor size measured on accumulated images (cm)
Tumor size measured in pathology(cm)
Tumor size measured on still images on peak time (cm)
Tumor size measured in pathology(cm)
Tumor size measured on MRI (cm)
Tumor size measured in pathology(cm)

Figure 3

Table 1 The average rank of three types of ultrasonographic images considered by experts (*Table a*) and beginners (*Table b*)

a

	average rank
P	1.34
A	2.22
S	2.44

b

	average rank
P	1.72
A	1.85
S	2.43

* : Statistically significant

n.s. : Not significant

P : Parametric images

A : Accumulated images

S : Still images on peak time

Table 2 Differences in the tumor size between the ultrasonographic images and the pathology

	Differences from the pathology (cm)			Correlation to pathology	
	Mean	Range	SD	r	95%CI
P	0.690	–1.535 - 3.285	0.847	0.664	0.139 - 0.846
A	0.336	–2.230 - 2.900	0.846	0.630	0.242 - 0.808
S	0.568	–2.305 - 3.105	0.909	0.717	0.481 - 0.843
MRI	–0.016	–1.435 - 0.938	0.543	0.915	0.848 - 0.952

The correlation between the three types of ultrasonographic images was substantial. MRI showed a higher correlation with the pathology than the ultrasonographic images.

95%CI 95% confidence interval, *SD* Standard deviation, *r* interclass correlation coefficient, *P* parametric images, *A* accumulated images, *S* still images on peak time

Table 3 Differences in the tumor size measured by experts and beginners

	Differences between two operators (cm)			Correlation between two operators	
	Mean	Range	SD	r	95%CI
P	0.207	−0.910 - 2.180	0.619	0.873	0.762 - 0.931
A	0.096	−1.530 - 1.670	0.733	0.807	0.650 - 0.894
S	−0.120	−1.370 - 1.980	0.580	0.880	0.782 - 0.934

The correlation between the tumor diameter determined by the experts and beginners using the three ultrasonographic images was almost perfect. There were no significant differences between the parametric images and conventional analysis images.

95%CI 95% confidence interval, *SD* Standard deviation, *r* interclass correlation coefficient, *P* parametric images, *A* accumulated images, *S* still images on peak time