Original Article

Contrast-enhanced ultrasound of breast tumors: an initial experience

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Abstract

Background: The increase of neoadjuvant treatment for breast cancer creates a capacity challenge as response evaluation by magnetic resonance imaging (MRI) is a limited resource. Contrast-enhanced ultrasound (CEUS) has been proposed as an alternative imaging strategy.

Purpose: To get experience with examination of malignant breast tumors with CEUS and evaluate the potential for future use in response evaluation of neoadjuvant treatment.

Material and methods: In this pilot study, the dynamic contrast-enhancement of ultrasound and MRI examinations were analyzed in 14 women with histologically verified breast cancer.

Results: Analysis of the time intensity curve of CEUS demonstrated the difference between tumor and normal tissue. The peak intensity was five times higher in tumor tissue (mean increase 397%, 95% CI 250–545). The curve was steeper for tumor tissue (mean 1.76, 95% CI 1.26–2.26) than for normal tissue (mean 0.43, 95% CI 0.24–0.62).

Conclusion: CEUS is a feasible method of examining blood flow in malignant breast tumors.

Keywords

Breast, ultrasound, contrast agents-intravenous, neoplasms-primary, tissue characterization

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Introduction

Mammography and ultrasound are the most important imaging modalities for breast tumors. Contrast-enhanced magnetic resonance imaging (MRI) is used in cases where ultrasound and mammography are insufficient, to screen for hereditary breast cancer, and to map the tumor extent before and during neoadjuvant treatment.

Neoadjuvant treatment is chemotherapy or endocrine therapy used prior to local treatment with surgery and/or radiation therapy both in locally advanced disease and to reduce large tumors.

MRI examination gives a good overview of both breasts and axillae and is the current gold standard in response evaluation in neoadjuvant treatment. An important part of the examination is analysis of the dynamic contrast enhancement in the tumor tissue. MRI-contrast initially stays in the blood vessels and diffuses into the interstitial space over time. The time density of the contrast curve is limited, with acquisitions every half minute. The patient must lie still for about 40 min in a prone position during the examination. There are contraindications for the MRI examination such as allergy, renal failure, medical implants, and claustrophobia.

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An increase in neoadjuvant treatment means an increase in the demand for MRI, and capacity has become an issue. There is a need for alternative imaging modalities, preferably less time consuming and more cost effective.

Use of contrast-enhanced ultrasound (CEUS) has proposed as an alternative imaging strategy as the method gives both morphological and functional information. Quantitative parameters from the examination can be used in the evaluation.[1,2] The contrast consists of small gas bobbles circulating in the blood without diffusion into the interstitial space, even in pathological blood vessels of a tumor. The ultrasound waves destroy the bobbles and the gas is eliminated through the lungs. Where MRI is limited by low time density in the acquisition of dynamic contrast-enhancement curves, continuous recording is current practice in CEUS. The patient is examined in supine position, and the duration with preparations is about 15 min.

There are few and rare side effects of the contrast media. Contraindications include severe pulmonary hypertension, uncontrolled hypertension, right-left shunt, adult respiratory distress syndrome, combination with dobutamine in patients with cardiovascular instability, and allergy to sulfur hexafluoride.[3]

Recent studies have shown good correlation of tumor size measured with CEUS and MRI both before and after neoadjuvant treatment.[4] CEUS seems to be a promising method to monitor response during and after neoadjuvant treatment.[5–7]

CEUS is evolving as an imaging technique in breast imaging.[6] The method is an active field of research and is not yet recommended for clinical use according to European Federation of Societies for Ultrasound in Medicine and Biology.[8]

The aims of this pilot study were to gather experience with examination of malignant breast tumors with CEUS, to investigate whether CEUS of the breast can be performed with readily available equipment, and to evaluate the potential for future use of CEUS in response evaluation of neoadjuvant treatment.

Material and methods

Patients from a single breast diagnostic center with suspected malignant breast tumor and scheduled MRI examination were invited to participate, and informed consent was obtained. Sixteen patients were recruited and included (June 2019–January 2020). Two patients were excluded (benign tumor and error in the saving of imaging information). Examinations of 14 histologically verified tumors were analyzed; 10 invasive carcinoma no specific type, 2 mucinous carcinoma, 2 invasive lobular carcinoma.

CEUS was performed with Logic E9 (GE Healthcare, Wauwatosa, WI, USA) with linear transducer (9 Hz, GE Healthcare). The plane for contrast evaluation was chosen from mammography and B-mode ultrasound. We used dual screen to show both B-mode and contrast image and maintained a steady probe position during the recording. 2.4 mL contrast, SonoVue (Bracco, Milan, Italy), was given as a single venous bolus from the arm, followed by the injection of 10 mL saline (0.9% NaCl). Record mode was activated before the contrast reached the tumor and continued for 60–90 s. Post-processing was performed immediately on the ultrasound machine (Logiq TIC software). The average intensity measured in a region of interest in tumor tissue and in normal tissue was displayed as time intensity curves (TIC). The curves illustrate signal intensity (dB) over time (Figure 1). We chose the TIC parameters peak intensity (PI), time to peak (TTP), and gradient and maximum gradient from the wash-in phase of the curve. The gradient is the overall rise of the curve and the maximum gradient is the steepest part of the curve. TTP is the time at witch contrast concentration reaches maximum. Measurements and analyses were exported to the picture archiving and communication system.

MRI was performed on a 1.5 Tesla Siemens Aera (Siemens Medical Solutions, Mountain View, CA), with a dedicated breast coil and standard protocol (Tra: T1_fl3D/T2fs/Diff, contrast-enhanced Tra/Sag: T1_fl3D). We used gadolinium-based contrast media (Clariscan, GE Healthcare, 0.5 mmol/ml). Post-processing was performed on a workstation (syngo.via, Siemens Healthineers). The variables PI, TTP, and gradient were included in the analysis.

The data was investigated with use of descriptive statistics, and TIC parameters of tumor and adjacent normal tissue were compared with a 2-tailed t-test for normally distributed continuous data. The use of relative measures (mean increase in percent of baseline value, gradient) enabled a comparison between the modalities. The contrast curves of MRI and CEUS cannot be compared directly as different traits are imaged and the time density is different.

Results

The TIC parameters' peak intensity, gradient, and maximum gradient were significantly increased for tumor tissue compared to normal tissue in our patients (2-tailed t-test, $p < .05$), as shown in Table 1. Peak intensity was five times higher in tumor tissue compared to normal tissue (mean increase 397%, 95% CI 250–545). The curve was steeper for tumor tissue (mean 1.76, 95% CI 1.26–2.26) than for normal tissue (mean 0.43, 95% CI 0.24–0.62).

At MRI, all contrast curve variables (PI, TTP, and gradient) showed significant difference between tumor tissue and normal tissue (2-tailed t-test, $p < .05$), as shown in Table 1. Peak intensity of MRI was six times higher for tumor tissue compared to normal tissue (mean increase 502%, 95% CI 348–657).

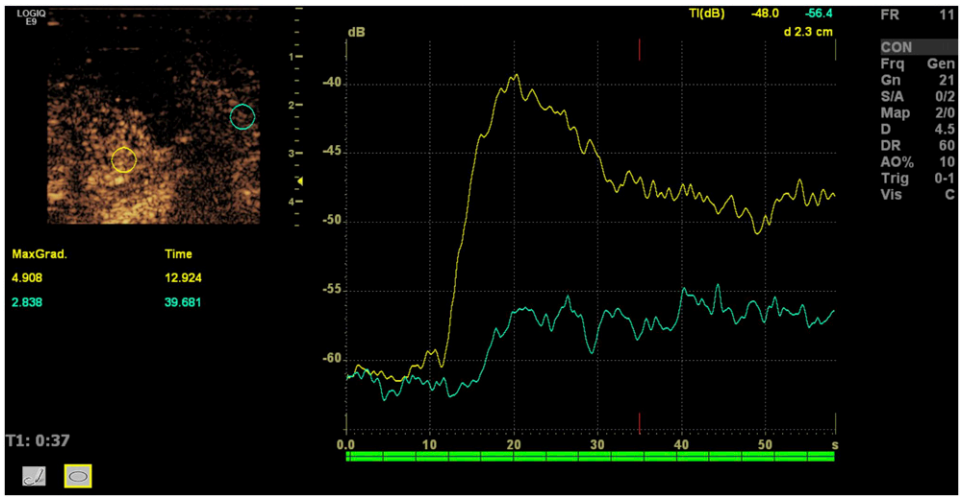

Figure 1. Contrast-enhanced ultrasound of a malignant breast tumor. Yellow curve represents dynamic contrast enhancement in the tumor and green curve represents adjacent normal breast tissue (dB/sec).

Table 1. Time intensity curve parameters from contrast-enhanced ultrasound and contrast-enhanced magnetic resonance imaging of breast tumors and normal adjacent tissue. 2-tailed t-test.

		Tumor	Normal tissue	
		Mean (95% CI)	Mean (95% CI)	*p*
CEUS	Peak intensity (dB)	17.0 (13.6–20.5)	5.8 (3.9–7.7)	<.001
	Time to peak (s)	10.9 (8.3–13.5)	18.7 (11.8–25.6)	.009
	Gradient	1.76 (1.26–2.26)	0.43 (0.24–0.62)	<.001
	Maximum gradient	6.46 (5.01–7.90)	3.58 (2.29–4.86)	.006
MRI	Peak signal intensity	155.9 (136.5–175.2)	41.6 (28.0–55.2)	<.001
	Time to peak (s)	208 (164–253)	322 (265–378)	.002
	Gradient	0.83 (0.64–1.03)	0.12 (0.09–0.16)	<.001

CEUS: contrast-enhanced ultrasound; MRI: magnetic resonance imaging; dB: decibel; s: seconds.

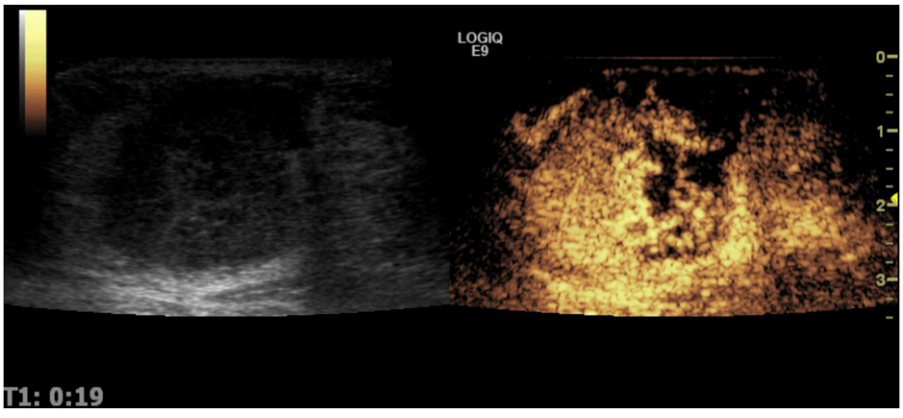

Figure 2. Malignant breast tumor in grayscale on the left and with contrast enhancement on the right. Areas without enhancement represent fibrosis or necrosis within the tumor.

Discussion

We found that CEUS of malignant breast tumors is feasible with available ultrasound equipment and contrast software. At ultrasound, the tumors could readily be identified with B-mode. Both recordings and contrast curves were easy to interpret. Our study showed significant difference in TIC parameters between tumor and normal adjacent tissue with

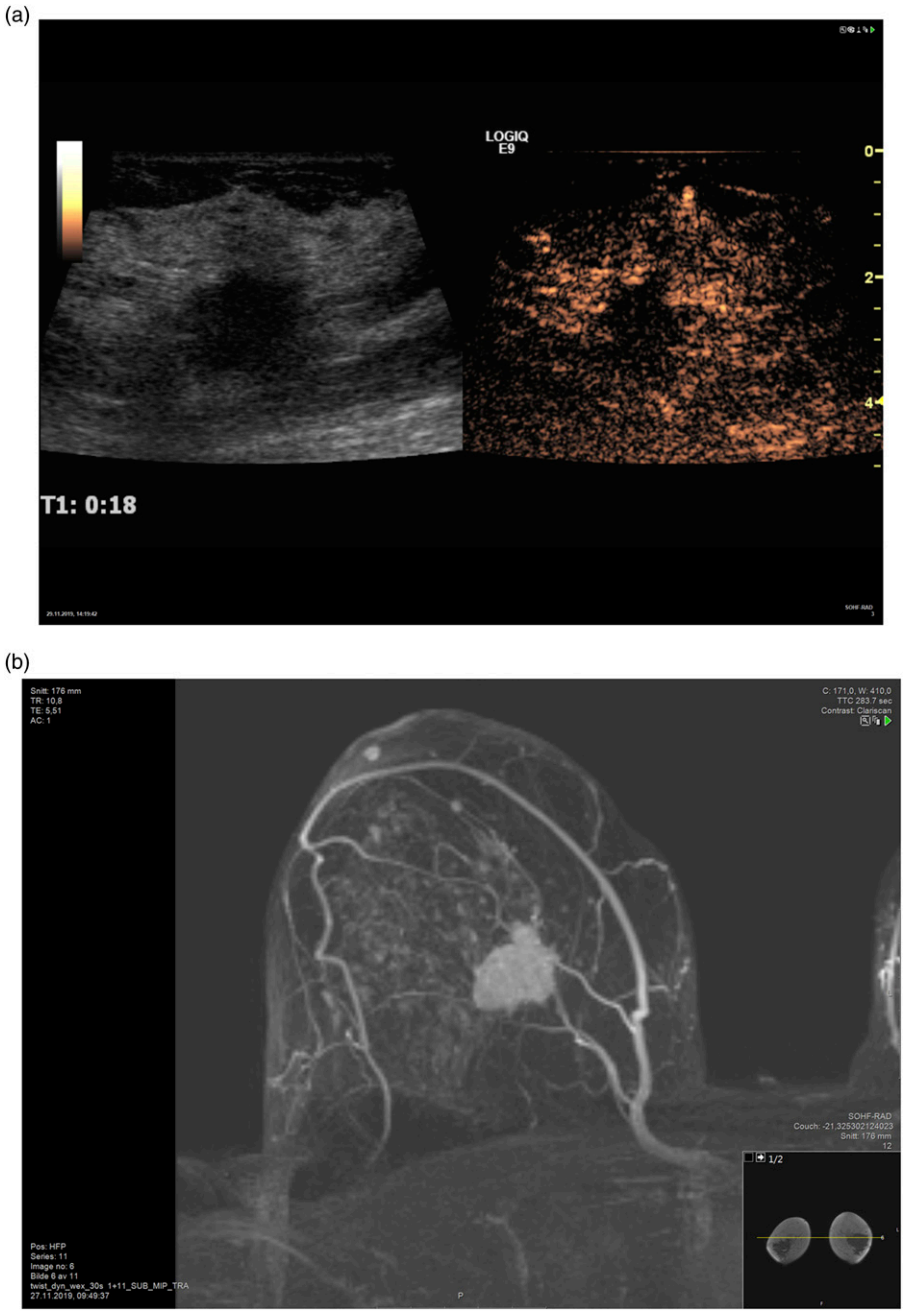

Figure 3. Hypoenhanced mass with poorly defined margins and hyperenhanced surrounding tissue (a). Corresponding magnetic resonance imaging (b).

CEUS and MRI, especially for the gradient and peak intensity, and are in line with other studies.[2,4]

The evaluation of tumor morphology was not included in this study. Nevertheless, our experience was that malignant tumors of the breast vary in appearance, composition, and contrast enhancement between patients. Chaotic organized network of branched blood vessels appear as heterogeneous and intense contrast enhancement. Arteriovenous shunting explains fast wash out of contrast.[9] Fibrotic tissue and degeneration can be seen as areas of tumor without enhancement (Figure 2). Some of the cases demonstrated peritumoral hyperenhancement (Figure 3). A recent study from Germany found a higher peak enhancement in the surrounding tissue of malignant tumors compared to benign lesions and scars, which may be due to peritumoral microvascularization.[10]

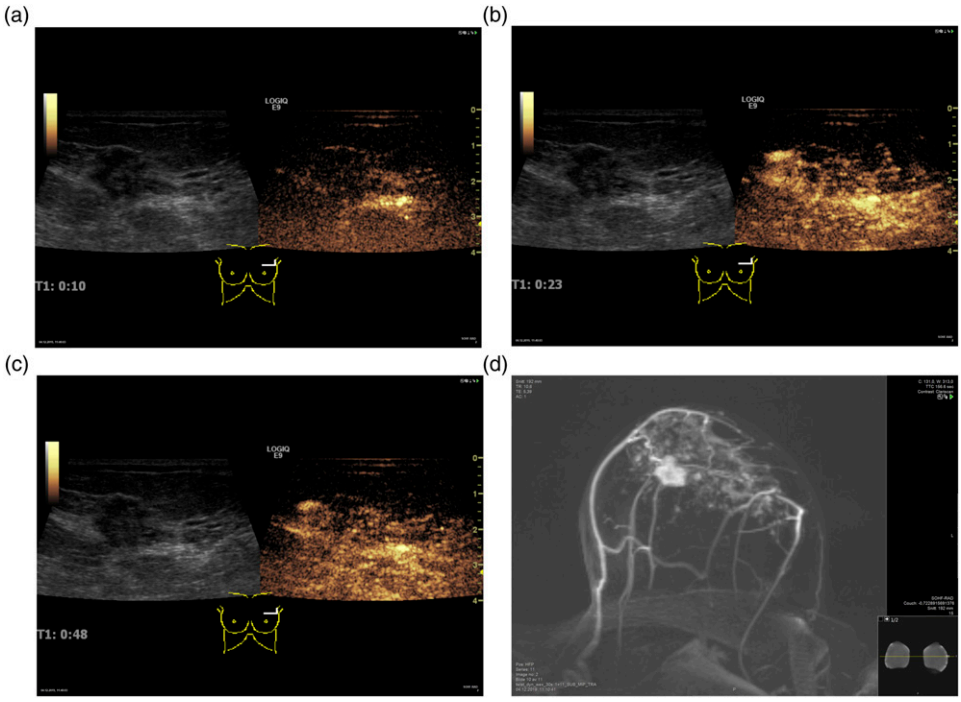

Figure 4. Contrast-enhanced ultrasound demonstrates a peripheral enhancing lesion with penetrating vessels after 10 (a), 23 (b), and 48 s (c). Corresponding magnetic resonance imaging (MIP) (d).

Features such as margins and contrast enhancement corresponded well for CEUS and MRI in this study (Figure 4).

Standardization of ultrasound examination can be a challenge. Only one breast can be examined at the time. The extent of large tumors can be hard to visualize. But to evaluate response to neoadjuvant treatment, there is no need for a complete coverage of the tumor. The comparison is done within the same patient, and the important feature is the difference between tumor tissue and normal adjacent tissue. A change in dynamic contrast curves after neoadjuvant treatment has been shown to correspond to treatment response.[5,7] A reduction in PI, gradient, and increase in TTP indicates response due to the decrease in blood flow and reduction of blood vessel density in tumor tissue. If a lack of response can be identified early in the course of the treatment, an alternative treatment strategy can be implemented to benefit the patient. Documentation of patient position and probe position will be very important as these can influence the accuracy of the examination.

In conclusion, contrast-enhanced ultrasound is a feasible method of examining blood flow in malignant breast tumors, and the method has potential for use in response evaluation of neoadjuvant treatment.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The Regional Ethics Committee gave their recommendation (REK 2019/354) and the local Data Protection Officer at Ostfold Hospital Trust approved of the project (11 June 2019).

Informed consent

The study participants gave informed written consent.

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