Feasibility of Imaging and Treatment Monitoring of Breast Lesions with Three-Dimensional Shear Wave Elastography


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Feasibility of Imaging and Treatment Monitoring of Breast Lesions with Three-Dimensional Shear Wave Elastography

Durchführbarkeit und Therapie-Monitoring von Brustläsionen mittels dreidimensionaler Scherwellen-Elastografie

Abstract

Purpose: Firstly to evaluate the feasibility and diagnostic performance of three-dimensional (3D) shear wave elastography (SWE) volume measurements in patients with breast lesions compared to breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) lesion volumes and 3D-US B-mode volumes. Secondly to assess the treatment monitoring performance of 3D-SWE in patients under neoadjuvant chemotherapy for breast cancer by comparing it to 3D-US lesion volume.

Materials and Methods: This prospective study was approved by the institutional review board. Informed consent was provided. 33 patients with 33 lesions were included. The feasibility of 3D-SWE was evaluated in 23 patients. In the 10 remaining patients receiving neoadjuvant chemotherapy, 3D-SWE was evaluated before and during treatment. Tumor volume and qualitative and quantitative elasticity analysis measurements were performed and compared to the tumor volume as estimated by 3D-US and DCE-MRI. Statistical analysis was performed using the Pearson correlation coefficient.

Results: 3D-SWE was feasible in patients with breast lesions. Tumor volume calculated with 3D-US and 3D-SWE showed very good and moderate concordances with DCE-MRI volume, respectively (Pearson correlation coefficients equal to \( \rho = r = 0.88, p < 0.00002 \) and \( \rho = r = 0.5, p = 0.32 \), respectively). Modification of tumor elasticity and heterogeneity was correlated with response to treatment. In good responders, elasticity and elasticity heterogeneity diminished.

Conclusion: Tumor 3D-US volume measurements showed very good concordance with DCE-MRI volume. 3D-SWE can provide valuable information: reduction of tissue stiffness during treatment could be a potential indicator of response.

Zusammenfassung


Ergebnisse: Die 3D-SWE war bei Patienten mit Brustläsionen machbar. Die Übereinstimmung des errechneten Tumorvolumens im Vergleich zum DCE-MRT-Volumen war für den 3D-US sehr gut (Pearson’s Korrelationskoeffizient \( r = 0.88, p = 0.00002 \)) und für die 3D-SWE moderat (\( r = 0.5, p = 0.32 \)). Eine Modifikation der Tumorlastizität und Heterogenität korrelierte mit dem Ansprechen auf die Therapie. Bei Patienten mit gutem Ansprechen verringerte sich die Elastizität und die elastische Heterogenität.

Schlussfolgerung: Die Volumenbestimmung des Tumors durch 3D-US zeigte eine sehr gute Über-
These preliminary results should be confirmed on a larger number of patients.

**Introduction**

Prognosis for women diagnosed with locally advanced breast cancer (clinical stages IIB through IIBB) has improved significantly over the past 20 years due to the efficacy of multimodal therapy even in patients with inflammatory breast cancer [1, 2]. A sensitive and specific method to identify tumor response to neoadjuvant chemotherapy (NACT) is mandatory because early recognition of non-responders facilitates change to a more effective treatment, minimizes toxicity, optimizes the timing of surgery and guides additional chemotherapy after surgery. Evaluation of response to treatment can be appreciated either by clinical examination or by imaging techniques such as mammography, ultrasound, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Reported agreement between the final response predictions and the responses measured by pathology had kappa values of 0.43 for clinical examination, 0.44 for mammography, 0.50 for sonography and 0.82 for DCE-MRI [3, 4]. DCE-MRI findings such as reduction in tumor volume, reductions in contrast uptake and contrast exchange rate were found to correlate significantly with pathologic complete response [5, 6]. Cost, availability and the need for intravenous injection of a contrast agent certainly represent drawbacks of this modality, along with some cases of claustrophobia or allergic reaction to contrast injection. Amongst the other modalities to assess treatment response, ultrasound yielded better accuracy compared to clinical examination or mammography. The largest tumor dimension is measured according to the RECIST criteria [7, 8]. However it does not always reflect tumor volume reduction accurately. Three-dimensional ultrasound (3D-US) could be useful for better appreciating morphological tumor reduction throughout treatment. However, it does not provide any “functional” information. Shear wave elastography (SWE) is a complementary technique providing information on tissue viscoelastic properties, as an adjunct to conventional morphological B-mode ultrasound imaging. Two-dimensional SWE (2D-SWE) provides qualitative and quantitative measurements in breast lesions by direct estimation of local stiffness of the tissue [9–14]. Indeed Cosgrove et al. [11] have demonstrated very high reproducibility of 2D-SWE with an intraclass correlation of 87.9% over 758 breast lesions and Berg et al. [12] showed an increase of specificity from 61.1% to 78.5% over 989 patients. Three-dimensional SWE (3D-SWE) has recently been applied in clinical practice and performed equally to 2D-SWE in distinguishing benign from malignant masses, and both techniques improved the specificity of B-mode ultrasound [15]. To the best of our knowledge, there has been no application of 3D-SWE for the evaluation of response to NACT in patients presenting with locally advanced breast cancer. The purpose of our study was firstly to evaluate the feasibility of three-dimensional (3D) shear wave elastography (SWE) volume measurements in patients with breast lesions compared to breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) lesion volumes and 3D-US B-mode lesion volumes. The second aim of the study was to assess the treatment monitoring performance of 3D-SWE in patients under neoadjuvant chemotherapy for breast cancer by comparing it to 3D-US B-mode lesion volumes.

**Materials and methods**

This prospective study was approved by the national ethics board (Comité de Protection des Personnes, “Ile de France II”, ID-RCS: 2010-A00663 – 36) and each included patient signed a written informed consent. Between December 2010 and March 2012, 33 patients aged 33 – 68 years (mean 57 ± 5 years), presenting with 33 breast lesions, were included. This study was conducted in two steps. First, the feasibility of 3D-SWE was evaluated in a group of patients presenting with a single breast lesion between 20 – 50 mm and scheduled for breast MRI (pre-operative staging of malignant lesions or follow-up of known lesions). 23 patients were included. The mean lesion diameter was 32 ± 5 mm (range: 22 to 48 mm). The histology is presented in Table 1. The 3D-SWE was performed within one month of the DCE-MRI. In this part of the study, lesion volumes with 3D-SWE and 3D-US were measured during NACT.

<table>
<thead>
<tr>
<th>histology</th>
<th>patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC NST</td>
<td>n = 15</td>
</tr>
<tr>
<td>ILC</td>
<td>n = 2</td>
</tr>
<tr>
<td>IDC NST +DCIS</td>
<td>n = 3</td>
</tr>
<tr>
<td>MUCINOUS</td>
<td>n = 1</td>
</tr>
<tr>
<td>FA</td>
<td>n = 1</td>
</tr>
<tr>
<td>PHYLLOID</td>
<td>n = 1</td>
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During the second part of the study, 10 patients with locally advanced breast cancer (lesion size ranging from 32 to 51 mm (mean 38 ± 5 mm)) scheduled to receive NACT were included. Patients presenting with multifocal disease or inflammatory cancer, patients already treated in the ipsilateral breast or patients with breast implants were excluded. Axillary lymph nodes were involved in five out of ten patients. Malignancy was established by core biopsy before 3D-SWE and DCE-MRI (Table 2). Histological diagnoses were performed by one pathologist with 20 years of experience in breast disease. Mammography, B-mode ultrasound and DCE-MRI were performed before the onset of NACT (baseline) and after the 4th (mid-treatment) and 8th cycles (end of treatment). All patients underwent 3D SWE before (baseline) and after the 2nd, 4th, 6th and 8th cycle of NACT. The time interval between imaging and NACT did not exceed one week. Surgery was performed during the 3 weeks after the end of NACT. Seven patients had conservative breast surgery after treatment (lum-
Table 2: Initial histological diagnosis and final pathologic grade of response according to Chevallier’s criteria for patients under NACT (n = 10).

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial histology</th>
<th>Grade of response</th>
</tr>
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<tbody>
<tr>
<td>Patient 1</td>
<td>IDC NST grade 2</td>
<td>2</td>
</tr>
<tr>
<td>Patient 2</td>
<td>IDC NST grade 3</td>
<td>3</td>
</tr>
<tr>
<td>Patient 3</td>
<td>IDC “basal like”</td>
<td>3</td>
</tr>
<tr>
<td>Patient 4</td>
<td>IDC NOS grade 2</td>
<td>2</td>
</tr>
<tr>
<td>Patient 5</td>
<td>IDC NOS grade 2</td>
<td>2</td>
</tr>
<tr>
<td>Patient 6</td>
<td>IDC NOS grade 3</td>
<td>2</td>
</tr>
<tr>
<td>Patient 7</td>
<td>ILC grade 3</td>
<td>3</td>
</tr>
<tr>
<td>Patient 8</td>
<td>IDC NOS grade 3</td>
<td>1</td>
</tr>
<tr>
<td>Patient 9</td>
<td>ILC grade 4</td>
<td>3</td>
</tr>
<tr>
<td>Patient 10</td>
<td>IDC NST+DCIS</td>
<td>4</td>
</tr>
</tbody>
</table>


pectomy and axillary lymph node dissection) and three had mastectomy with axillary lymph node dissection.

The standard neoadjuvant treatment protocol comprised 4 cycles of FEC 100 (epirubicin 100 mg/m² with 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²) every 21 days followed by 4 cycles of docetaxel 100 mg/m² every 21 days.

Results were compared to pathology of the surgical specimen using Chevallier’s criteria, with complete response defined as grade 1 (no residual tumor) or grade 2 (residual in situ carcinoma without any invasive component in the breast). Incomplete response corresponded to grade 3 (residual invasive carcinomatous cells associated with stromal alteration) or grade 4 (absence or no therapeutic effect, no modification of tumoral cells) (Table 2).

3D-US and 3D-SWE imaging

3D-US and 3D-SWE images were obtained using an ultrasound diagnostic imaging system called Aixplorer (SuperSonic Imagine, Aix en Provence, France). The system was equipped with a 2D mechanical wobbling g probe (SLV 16–5, 8 MHz) designed for conventional 3D-US and 3D-SWE imaging.

Both 3D-US and 3D-SWE were performed and interpreted by one of two radiologists (A.A., A.T.) with 10 and 20 years of breast imaging experience, respectively, and 4 years of shear wave elastography experience. The same radiologists also interpreted DCE-MRI and performed volume measurements.

Once the 3D acquisition was completed, the volume was displayed in three orthogonal slice planes (axial, sagittal and coronal) along with a 3D display showing relative positions. Measurements of the tumor maximal sizes were performed in the central-axial and central-transverse planes defined by the radiologist. Tumor volumes were calculated using an ellipsoid defined by equation 1, in which \( d_a, d_s, d_c \) represent the tumor maximal sizes measured in the axial, transverse and coronal planes, respectively:

\[
V = \frac{\pi d_a d_s d_c}{6}
\]  

Using the same probe, 3D-SWE acquisitions were performed along the central-axial and central-sagittal plane of the tumors. Each pixel within the 3D elasticity volume was quantified in kilopascals (kPa) and color-coded from dark blue (softer) to red (harder). The color scale was fixed at a maximum of 180 kPa. At the end of the acquisition, three orthogonal planes (axial, transverse and coronal) were presented on a 3D display. The system offered quantitative analysis of tissue stiffness at every single pixel within the 3D volume, obtained by calculating the mean elasticity value within a circular region of interest (ROI, also called Q-Box\(^6\)) covering a 2 mm diameter circle in the stiffest part of the lesion. The mean ratio (defined as the ratio of stiffness in the mass to the adjacent fat) and standard deviation (indicator of tissue stiffness heterogeneity within the lesion) were also reported.

Tumor elasticity volumes were obtained by segmenting all three planes (axial, transverse and coronal) of 3D-SWE acquisitions. The segmentation was performed automatically using Matlab\(^6\)-based image processing software (MathWorks, USA). The segmentation threshold was set up to 55 kPa to distinguish between benign and malignant tissue, as reported in previously published work [16]. Then maximal dimensions in all three planes were derived and tumor elasticity volume was calculated according to equation 1. An example of segmentation is presented in Fig. 1.

MRI examination

All MRI sequences were performed on a 1.5-T unit (Symphony, Siemens, Erlangen, Germany) using a dedicated 4-channel breast coil and a standard protocol including morphologic and dynamic sequences in accordance with the recommendations of the European Society of Breast Imaging (EUSOBI) and the European Society of Breast Cancer Specialists (EUSOMA) [17, 18].

Statistical analysis

For the feasibility part of the study, a linear regression was carried out between all derived volumes. The Pearson correlation coefficient \( p \) was calculated to assess the concordance between the 3D-US volumes, 3D-SWE volumes and DCE-MRI volumes for each lesion (23 lesions) as well as unpaired Student’s t-test, to compare volume measurements from the 3 modalities. The ratios between the 3D-US and DCE-MRI, 3D-SWE and 3D-US, and 3D-SWE and DCE-MRI volumes for each lesion were also calculated as well as the mean ratio and standard deviation for all lesions. 3D-US and 3D-SWE lesion volumes were correlated to DCE-MRI. For the treatment monitoring part of the study, ratios between volumes before NACT and during NACT were calculated as well as the elasticity and elasticity standard deviation ratios (representing the heterogeneity of elasticity within the lesion). Pearson correlation coefficients were calculated between volume ratios and elasticity ratios and volume ratios and elasticity standard deviation ratios. The changes of tumor stiffness were expressed as percentage (the elasticity before NACT being the reference).

Results

During the feasibility part, stiffness values (according to pathology) and standard deviations of the 23 lesions studied with 3D-SWE were in accordance with the values reported in the literature (Fig. 2). The axial plane of 3D-SWE gave an almost identical to 2D SWE aspect whereas the coronal view of 3D-SWE permitted a more thorough analysis of perilesional stiffness (Fig. 3). 3D-US volumes were smaller than the DCE-MRI and 3D-SWE volumes (mean ratio and standard deviation of 38 ± 26% and 72 ± 51%, respectively), while 3D-SWE and DCE-MRI provided similar estimations of volumes (mean ratio and standard deviation of 2 ± 43%) (Fig. 4, Table 3).

Treatment monitoring results are summarized in Fig. 5 and Table 4, presenting the lesion volume changes, the Young’s
modulus changes, the elasticity ratio (ratio between elasticity before the onset and during treatment) and the elasticity standard deviation ratio before and during neoadjuvant treatment. Larger tumors were found to present more heterogeneous stiffness patterns and higher values of Young’s modulus.

The Pearson correlation coefficient between lesion volume ratio changes (ratio between volumes measured before NACT and during NACT) and tissue elasticity ratio and elasticity standard deviation were 0.39 and 0.62, respectively. The response to treatment according to Chevallier’s criteria is presented in Table 2. Two patients responded completely to treatment, six had a partial response in the final surgical specimen and two did not present a significant therapeutic effect.

Table 3 Pearson correlation coefficients between 3D-US, 3D-SWE and MR-DCE volumes, unpaired Student t-test, and mean and standard deviation of volume ratios.

<table>
<thead>
<tr>
<th></th>
<th>correlation coefficient</th>
<th>confidence interval at 95%</th>
<th>student t-test: p-value</th>
<th>ratio mean and standard deviation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-US versus MR-DCE (reference)</td>
<td>0.88</td>
<td>[0.82 – 0.94]</td>
<td>p &lt; 0.00003</td>
<td>−38 ± 26 %</td>
</tr>
<tr>
<td>3D-SWE versus 3D-US (reference)</td>
<td>0.77</td>
<td>[0.71 – 0.83]</td>
<td>p &lt; 0.00005</td>
<td>72 ± 51 %</td>
</tr>
<tr>
<td>3D-SWE versus MR-DCE (reference)</td>
<td>0.50</td>
<td>[0.20 – 0.80]</td>
<td>p = 0.32</td>
<td>2 ± 43 %</td>
</tr>
</tbody>
</table>
Discussion

During the feasibility part of this pilot study, there was an almost perfect agreement between the 3D-US volumes and those of DCE-MRI ($\rho = 0.88$), moderate agreement between DCE-MRI and 3D-SWE volumes ($\rho = 0.50$), and good agreement between 3D-US and 3D-SWE volumes ($\rho = 0.77$). The differences in volume measurements between DCE-MRI, 3D-SWE and 3D-US may be related to the different tissue properties/functions assessed by these imaging techniques. Indeed DCE-MRI imaging evaluates soft tissue vascularization, whereas SWE is linked to tissue elasticity and US relates to structural and morphological soft tissue changes. Regional lesion stiffness as imaged by SWE may correspond to lesion stiffness itself as well as peritumoral desmoplastic reaction and/or edema or inflammation, exhibiting increased stiffness, due to the presence of fibrosis [19] and increased microvascularization. It has been reported that US volume measurements may underestimate lesion size [20], 3D-US underestimated the tumor volume by a factor of 0.38, while 3D-SWE had a closer volume estimation even though the estimations were less accurate.
correlated to the DCE-MRI volumes. Therefore, the association of 3D-US and 3D-SWE could potentially be used to monitor lesion volume changes during NACT, as combining results may provide more accurate lesion volume estimation.

Our findings of 3D-SWE elasticity in cases of large cancers (higher values of stiffness and more heterogeneous stiffness pattern) were in concordance with the results of Chamming’s et al. [19]. Indeed this team reported that the elasticity of breast cancer measured with 2D-SWE is linked to its size and that stiffness changes with tumor growth are correlated with pathological changes. In another published study evaluating SWE findings with respect to histologic prognostic factors in malignant lesions [21], more heterogeneous SWE imaging and more elevated Young’s modulus were correlated with a more aggressive tumor biological profile. The heterogeneous stiffness patterns and higher values of Young’s modulus we experienced in larger tumors were possibly due to tumor stromal heterogeneity itself. Moreover, 3D-SWE was evaluated by Youk et al. [22] and was found to give similar results as 2D with regard to the differentiation between benign and malignant lesions, meaning that malignancies presented similar features on 3D-SWE and 2D-SWE and we observed the same results (Fig. 3).

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**Fig. 4** Volume measured by MRI, 3D-US and 3D-SWE for 23 lesions included in the feasibility part of the study.

**Abb. 4** Volumenbestimmungen durch MRT, 3D-US und 3D-SWE bei 23 Läsionen, die in die Machbarkeitsstudie eingeschlossen wurden.

**Fig. 5**

*a* Volume changes for each patient during NACT treatment.  
*b* Elasticity (or Young’s modulus) changes in kPa for each patient during treatment.  
*c* Elasticity (or Young’s modulus) ratios (ratio between elasticity during the treatment and elasticity before the treatment) in % for each patient during treatment.  
*d* Elasticity (or Young’s modulus) standard deviation ratios (ratio between standard deviation during the treatment and standard deviation before the treatment) in % for each patient during treatment.

**Abb. 5**

*a* Volumenänderungen für jeden Patienten nach NACT-Therapie.  
*b* Änderungen der Elastizität (oder des Elastizitätsmoduls Z) in kPa für jeden Patienten während der Therapie.  
*c* Ratio der Elastizität (oder des Elastizitätsmoduls Z) in % für jeden Patienten während der Therapie (Ratio zwischen der Elastizität während der Therapie und der Elastizität vor Therapie).  
*d* Standardabweichung der Ratios der Elastizität (oder des Elastizitätsmoduls Z) in % für jeden Patienten während der Therapie.
In the second part of our feasibility study, even if the number of patients was limited, we identified the following criteria that could be used to evaluate response to treatment:

Tumor shrinkage was associated with a decrease in stiffness (softening of the tumor) and a more homogeneous color pattern (red coding becoming progressively blue) (Fig. 6). Indeed, eight out of ten lesions presented a decrease in lesion stiffness (89 ± 36% softening of the tumor) and stiffness heterogeneity (75 ± 14%) during treatment. Interestingly, tissue elasticity heterogeneity was better correlated to volume changes than stiffness itself (Pearson correlation coefficients 0.39 and 0.62, respectively). Complete responders presented a rapid decrease of lesion volume and a rapid decrease in Young’s modulus and elasticity standard deviation after the second cycle of NACT. Visual appreciation of the color-coded elastogram was proved to be useful in these cases: clearly heterogeneous, stiff, red-coded lesions before...
treatment presented a homogeneous blue, soft elasticity pattern after 2 cycles. No significant decrease of volume linked to steady or increasing stiffness (5 ± 24%) and standard deviation (16 ± 19%) indicated poor response (patients 9 and 10 in Table 2) (Fig. 7). Partial response (Chevalier’s grade 3) presented variability in elasticity modifications in different patients. For example, patient 3 had a significant volume decrease (94%) and only 16% modification of elasticity, possibly due to intra and peritumoral heterogenous stromal alteration. Hence a new protocol study over a large number of patients should be performed to combine multi-parameters to confirm the prognosis of NACT success.

3D-SWE volumes offered a multi-planar view of the tumor elasticity distribution. Additional appreciation of tumor spiculation in the surrounding parenchyma could be observed by navigating through tumor slices and more particularly in the coronal planes (Fig. 8).

To our knowledge, three studies have evaluated ultrasound elastography in women presenting locally advanced breast cancer and undergoing NACT [23-25]. Initial published results were promising and also showed a decrease in stiffness and statistically significant relationship with pathological response of invasive breast cancer to NACT. This is the first attempt to evaluate the feasibility of 3D-SWE and its potential role to predict response to NACT by quantifying the 3D softening of tumors during treatment. This elasticity change was found to be important with a mean softening of 67% on the ten patients (with a minimum of −22%, hardening and a maximum of 97%, softening).

Our study presents two limitations. First of all the number of patients included is small to extract statistically significant results. This study was a “feasibility study” to evaluate the feasibility and assess the preliminary performance of the 3D-SWE technique in the monitoring of breast cancer treatment. A second study is actually under approval by the ethics committee in our institution in order to confirm these findings in a larger number of patients. Secondly, tumor volume measurements on 3D-US and 3D-SWE were derived from an ellipsoid model, which may not be accurate for all tumors. However, correlation with DCE-MRI data was found to be satisfactory. The development of a software tool for tumor segmentation would result in more accurate 3D ultrasound and elastography tumor volume calculation.

In conclusion, 3D-SWE was feasible and 3D-SWE lesion volumes were well and moderately correlated to 3D-US and DCE-MRI lesion volumes, respectively. It also provided multi-planar information on the elasticity distribution inside and around the tumor as well as possible patterns of response to treatment. Concomitant, early, rapid decrease in lesion volume, stiffness and heterogeneity could potentially represent indicators of early response to NACT. Further studies are required in order to confirm these preliminary results.

References
1 Silvov WM. Locally advanced breast cancer. Curr Treat Options Oncol 2000; 1: 228–38