

# State of the Art: Contrast Enhanced 4D Ultrasound to Monitor or Assess Locoregional Therapies

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## Abstract

Locoregional therapies (LRTs) are an essential management tool in the treatment of primary liver cancers or metastatic liver disease. LRTs include curative and palliative modalities. Monitoring treatment response of LRTs is crucial for maximizing benefit and improving clinical outcomes. Clinical use of contrast-enhanced ultrasound (CEUS) was introduced more than two decades ago. Its portability, cost effectiveness, lack of contraindications and safety make it an ideal tool for treatment monitoring in numerous situations. Two-dimensional dynamic CEUS has been proved to be equivalent to the current imaging standard in the guidance of LRTs, assessment of their adequacy, and detection of early tumor recurrence. Recent technical advances in ultrasound transducers and image processing have made 3D CEUS scanning widely available on most commercial ultrasound systems. 3D scanning offers a broad multiplanar view of anatomic structures, overcoming many limitations of two-dimensional scanning. Furthermore, many ultrasound systems provide real-time dynamic 3D CEUS, also known as 4D CEUS. Volumetric CEUS has shown to perform better than 2D CEUS in the assessment and monitoring of some LRTs. CEUS presents a valid alternative to the current imaging standards with reduced cost and decreased risk of complications. Future efforts will be directed toward refining the utility of 4D CEUS through approaches such as multi-parametric quantitative analysis and machine learning algorithms.

## Keywords

- ▶ contrast-enhanced ultrasound
- ▶ 4D
- ▶ volumetric imaging
- ▶ hepatocellular carcinoma
- ▶ locoregional therapy
- ▶ treatment response assessment

Locoregional therapies (LRTs) are an essential management tool in the treatment of primary or metastatic liver cancers.<sup>1</sup> Although LRTs have demonstrated improved survival, they are associated with high recurrence rates.<sup>1,2</sup> Consequently, early response assessment and identification of recurrence is key to improving clinical outcomes. Tumor viability is determined by arterial enhancement patterns on contrast-enhanced cross-sectional imaging. Modified response evaluation criteria in solid tumors (mRECIST) are currently the most validated criteria for response assessment.<sup>3</sup> The American College of Radiology has developed

treatment response evaluation criteria as part of the Liver Imaging Reporting and Data System (LI-RADS).<sup>4</sup> The mentioned criteria are validated for MRI and CT imaging. Contrast-enhanced ultrasound (CEUS) provides an analogous means of examining the tumor viability.<sup>5,6</sup> The CEUS LI-RADS<sup>7</sup> has defined criteria for HCC diagnosis in high-risk patients, it incorporates lesion size, arterial phase hyper-enhancement (APHE), and washout dynamics to define the probability of malignancy in focal liver lesions (FLL). Its categories range from definitely benign (LR-1) to definitely malignant (LR-5). Recently, treatment response assessment

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criteria in HCC have been described,<sup>8</sup> however they are yet to be validated.

Compared with CT and MRI, ultrasound is cost-effective, readily available, does not involve radiation exposure, and is not limited by contrast reactions making it well-suited for longitudinal treatment response monitoring. It is also a dynamic technique that allows real-time examination of contrast enhancement pattern with higher temporal resolution than CT and MRI. Ultrasound contrast agents are microbubbles comprised of high molecular weight gases encapsulated in a shell of lipid, protein, surfactant, or polymer. The size of the microbubbles (<10 μm) enables them to reach the systemic circulation through the pulmonary capillaries.<sup>9</sup> The acoustic impedance mismatch and differences in compressibility between the gas inside the microbubbles and the surrounding tissues make them effective echo-enhancers.

Two-dimensional imaging is inherently limited in its assessment of tumors as a single imaging plane and does not show the entirety of a tumor. This factor increases operator dependence and consequently, measurements based on 2D imaging can be inaccurate. Moreover, it can be challenging to locate the same imaging plane over multiple exams reducing reproducibility during longitudinal response monitoring. However, recent advances in 3D CEUS have enabled a multiplanar approach in anatomical assessment, pathology, and enhancement patterns in tissues.<sup>10</sup> Furthermore, 4D CEUS shows perfusion dynamics in real time and enables volumetric examination of the enhancement pattern in three phases: arterial, portal, and late venous. In this review, we will discuss the recent advances in using 4D CEUS focusing on the assessment of therapeutic response of hepatocellular carcinoma to LRTs.

### Quantitative Contrast-enhanced Ultrasound (CEUS)

A standard CEUS exam begins with B-mode scanning to locate the area of interest. Nonlinear contrast-image packages are then used at lower mechanical indexes (<0.3) to avoid microbubble contrast agent destruction while detecting nonlinear signals generated from the agents. Imaging is often performed in dual B-mode/nonlinear imaging to provide both anatomical guidance and realtime visualization of microbubble perfusion. For liver imaging, the hepatic arterial phase starts 10–20 seconds following injection and lasts up to 30–45. The extent of the lesional microvasculature is best visualized in this phase. The portal venous phase, when maximal enhancement of the normal liver parenchyma is seen, overlaps with the end of the arterial and lasts up to 120 seconds after contrast injection. The late phase lasts until the contrast agent is cleared from the circulation and usually ends around 4–6 minutes after injection.<sup>11,12</sup> CEUS is recommended for characterization of focal liver lesions that are inconclusive on contrast-enhanced CT/MRI and in patients with contraindications against those modalities such as renal insufficiency.<sup>11</sup> Additionally, it can help visualize a poorly identified lesion or select a lesion among multiple ones when

a liver biopsy is needed.<sup>11</sup> Despite the advantageous spatial and temporal resolutions of CEUS, it still has several limitations. It is limited in evaluating subdiaphragmatic or deep-seated lesions, lesions smaller than 10 mm, and lesions in patients with large body habitus or incapable of holding their breath.<sup>13</sup>

Quantitative CEUS entails measuring the wash-in and wash-out kinetics of a region of interest (ROI) through time-intensity curves (TIC). The ROI can be placed either manually or with the help of segmentation algorithms. The TIC represents the average intensity of the ROI as a function of time after the contrast injection. Several quantitative parameters of the blood flow and volume can be extracted from the TIC to characterize the vasculature of the lesion.<sup>14</sup> Peak intensity, area under the wash-in curve, area under the wash-out curve, and area under the curve describe the fractional blood volume in the lesion. Time to peak and mean transit time relate to the blood flow through the lesion. These parameters may provide a more accurate way to characterize FLL or HCC treatment response compared with qualitative assessment.

### 2D CEUS in LRT Response Monitoring

Two-dimensional CEUS is well established in characterizing the viability and malignancy of indeterminate liver lesions.<sup>11,15,16</sup> The CEUS LI-RADS<sup>7</sup> algorithm integrates lesion size and imaging features to determine the likelihood of malignancy in such lesions. Before and after LRTs, CEUS provides better tumor visualization than conventional gray-scale ultrasound leading to better real-time treatment guidance.<sup>17</sup> Additionally, visualization of tumor perfusion dynamics in real time facilitates examining tumor viability during procedures to confirm the treatment adequacy.<sup>5,6</sup> CEUS is not limited by artifacts produced by iodized oil or drug-eluting beads used in embolic therapies.<sup>18</sup> This enables clinicians to decide if retreatment is needed as early as the same treatment session, thus leading to better outcomes and minimizing the cost of care.

Thermal ablation is a widely used curative modality for early stages (BCLC 0–A) of hepatocellular carcinoma (HCC) and other liver malignancies.<sup>19</sup> CEUS guidance was found to cut down the time needed for RFA compared with other imaging modalities.<sup>20</sup> Within 5–10 minutes after RFA, CEUS accurately detected any areas of residual viability which could be treated in the same session, thus reducing required repeat ablation sessions and improving the effectiveness of the procedure.<sup>21</sup> A systematic review of multiple studies revealed that local tumor progression rates after CEUS-guided ablation were 0–12% during follow-up.<sup>22</sup> While immediate assessment post-ablation seems to be the most beneficial not just in treatment assessment but also in screening for post-procedural complications,<sup>23</sup> it still has its drawbacks. Gas produced during ablation may linger and obscure the tumor features.<sup>24</sup> Furthermore, reactive hyperemia post-ablation may be misdiagnosed as residual tumor.<sup>25</sup> Later time points of monitoring have been investigated in multiple reports.<sup>26</sup> CEUS at 24h post-ablation

had a specificity close to 100%, while its sensitivity ranged widely across studies. One-month CEUS exam after ablation had both high sensitivity (87–91%) and specificity (97–98%) and its diagnostic performance was equivalent or even better than contrast-enhanced CT.<sup>27</sup>

Transarterial chemoembolization (TACE) is a commonly used treatment for intermediate HCC patients who are not fit for surgery or ablation. It involves injection of chemotherapeutic agents along with embolizing microparticles to selectively occlude the blood supply and deliver chemotherapy to the tumor.<sup>1</sup> The current clinical standard for TACE response assessment is contrast-enhanced CT or MRI 4–6 weeks post-treatment. This delay in assessing treatment response is due to the artifacts caused by the inflammatory hyperemia and lipiodol in the treatment region.<sup>28</sup> Contrary to CT and MRI, CEUS can reliably distinguish viable tumor from post-procedural inflammatory hyperemia and is not limited by artifacts from lipiodol. Therefore, CEUS can be useful for assessing tumor response significantly earlier than the current standard. Additionally, CEUS has exceptional temporal resolution which allows it to detect small areas of viable tumor not appreciated on other cross-sectional imaging methods.<sup>29</sup> With one-month CT or MRI as the gold standard, CEUS in the 2 weeks following TACE has high sensitivity (93–100%) and variable specificity (65–100%) in detecting residual HCC.<sup>30–32</sup> An example of early CEUS response assessment of TACE is shown in ►Fig. 1. 2D CEUS has also been investigated as a means for predicting TACE outcomes prior to therapy.<sup>33</sup> In one study, pretreatment CEUS-derived vascular morphologic features were studied as predictors to HCC response after TACE.<sup>34</sup> Specific parameters included number of vessels (NV), number of branching points (NB), vessel-to-tissue ratio (VR), mean vessel length (VL), mean vessel tortuosity (VT), and mean vessel diameter (VD). Of those, NV, NB, and VR were found to be the most reliable and were used to establish the prediction model whose sensitivity, specificity, and accuracy were 89%, 82%, and 86% respectively. Such approach can be used for creating tailored treatment plans and potentially improving treatment outcome.

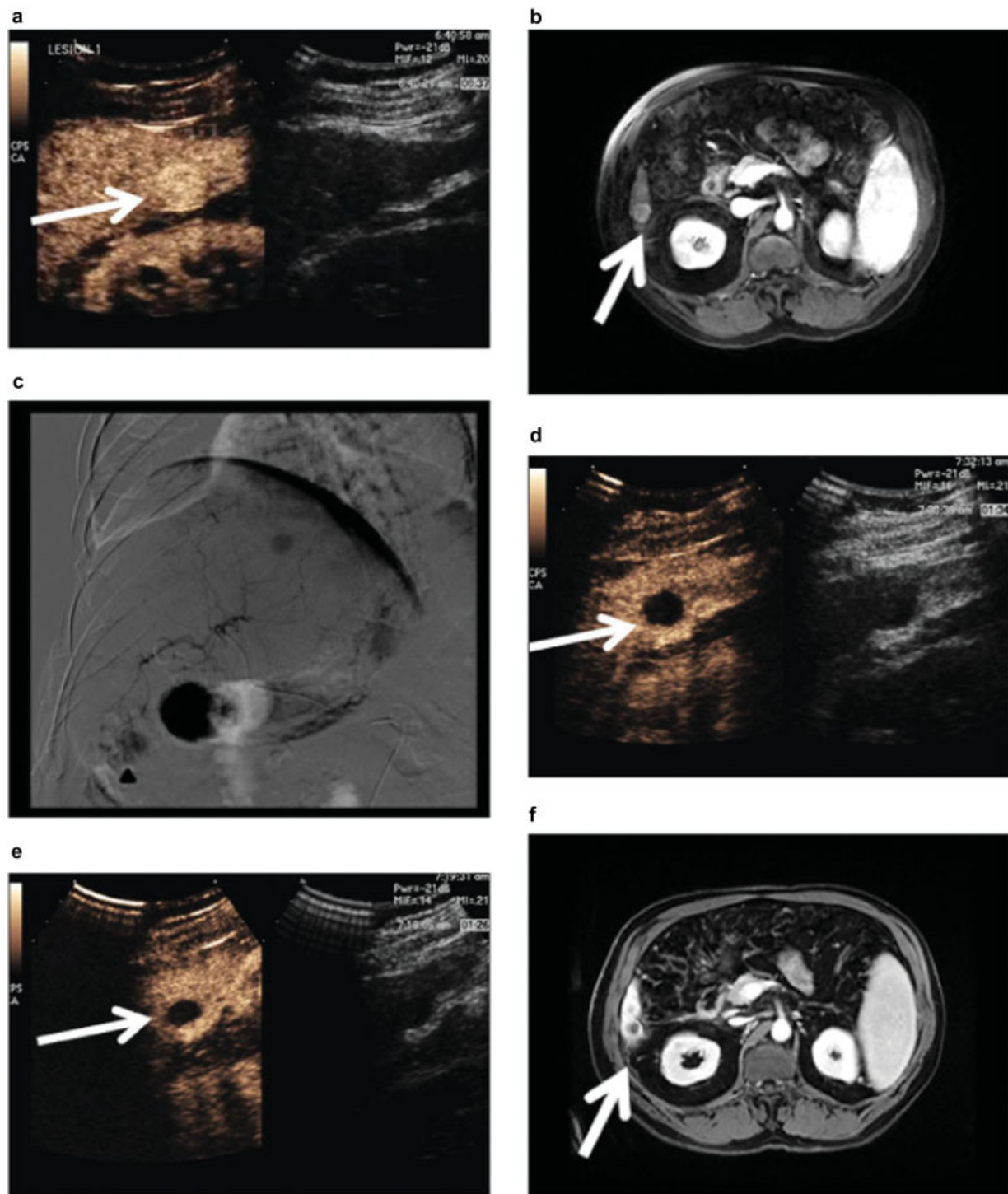
Transarterial radioembolization (TARE) is another treatment approach for intermediate or advanced stage HCC patients. Microsphere containing the radioactive isotope Yttrium-90 (Y-90) are selectively injected to the hepatic tumor region, delivering localized radiation to the tumor.<sup>35</sup> Tumor response to TARE is typically assessed 3–4 months post procedure using contrast enhanced MRI or CT to assess the full effect of treatment.<sup>36</sup> As part of an ongoing clinical trial, CEUS is being tested as an early way of evaluating HCC response to TARE.<sup>37</sup> Preliminary results have showed that reduction in tumor vascularity quantified by CEUS was associated with better mRECIST response categories and attributed to destruction of tumor vasculature.<sup>38</sup> These results align with prior studies using pretreatment computed tomography perfusion imaging parameters to predict HCC response to TARE.<sup>39</sup> Hepatic blood volume, hepatic perfusion index, and time to start, calculated from perfusion maps, were found to be predictive of progressive disease (PD) after TARE treatment.

### 3D CEUS in LRT Response Monitoring

Three-dimensional imaging provides an opportunity for increased perspectives to examine anatomic structures. It also minimizes operator dependency and artifacts caused by organ orientation and patient position during image acquisition.<sup>40</sup> Initially, 3D ultrasound was commonly used in gynecology, obstetrics, and cardiology.<sup>41</sup> Volumetric ultrasound imaging of solid tumors was initially challenging as there was insufficient echogenicity differences between lesions and the surrounding tissue to enable appropriate segmentation. CEUS provided this needed contrast and 3D CEUS enabled clinicians to capitalize on the superior spatial resolution of 3D imaging. Reports of 3D CEUS imaging of solid organs include lesions in the liver,<sup>42</sup> kidney,<sup>43</sup> prostate,<sup>44</sup> and breast.<sup>45</sup> Tumor vascularity is highly heterogeneous and more prone to sampling errors in 2D. Hence, 3D CEUS offers potential advantages in tumor imaging. Manipulation of slice thickness and intervals can detect enhancements that would be less conspicuous on a 2D CEUS scan.<sup>46</sup> As a result, 3D CEUS has been studied in the early determination of tumor response to local treatment.<sup>47–49</sup>

In thermal ablation of liver tumors, 3D CEUS has been examined as a means of guiding and confirming the adequacy of the procedure. A research group investigated the effectiveness of ablation when intra-procedural 3D CEUS was used to confirm technical success and guide further need for ablation.<sup>50</sup> Images were acquired 5–10 minutes after the ablation, using SonoVue (Bracco, Italy) as the contrast agent. The technique effectiveness rate was found to be 98.8%, which is an improvement on the rates reported using conventional 2D ultrasound. Similar to 2D CEUS, the adequacy of the ablation can be confirmed by the absence of any intralesional microbubble enhancement indicating the absence of blood flow and complete tumor necrosis. In 2009, Xu et al. published a study examining the utility of 3D CEUS in the assessment of LRTs efficacy. The study included 51 patients with either HCC or metastatic liver cancer and used SonoVue as the contrast agent. The follow-up times ranged from one to 13 days. The results showed that 3D CEUS improved the confidence of treatment response diagnosis compared with 2D CEUS.<sup>42</sup> The same group conducted a larger study with 90 HCC lesions in patients who underwent different types of LRTs with 3D CEUS at a wide range of time points after treatment (10 minutes to 28 months). 3D-CEUS increased the confidence in the diagnosis in almost 80% of cases. Moreover, it changed the management of 3% of the patients, while 2D CEUS did not change the management in any of the patients.<sup>51</sup>

Several other studies of response assessment have been performed at more established time points post-treatment. One research group used 3D CEUS, with Sonazoid (GE Healthcare, Norway) as the contrast agent, to assess the adequacy of high-intensity focused ultrasound ablation of HCC.<sup>52</sup> The 3D CEUS exams were performed immediately, one week, and one month post-ablation. The reference standard was either contrast-enhanced CT (CECT) or contrast-enhanced MRI obtained one week and one month post-ablation. The study reported high concordance between immediate 3D CEUS exams and the

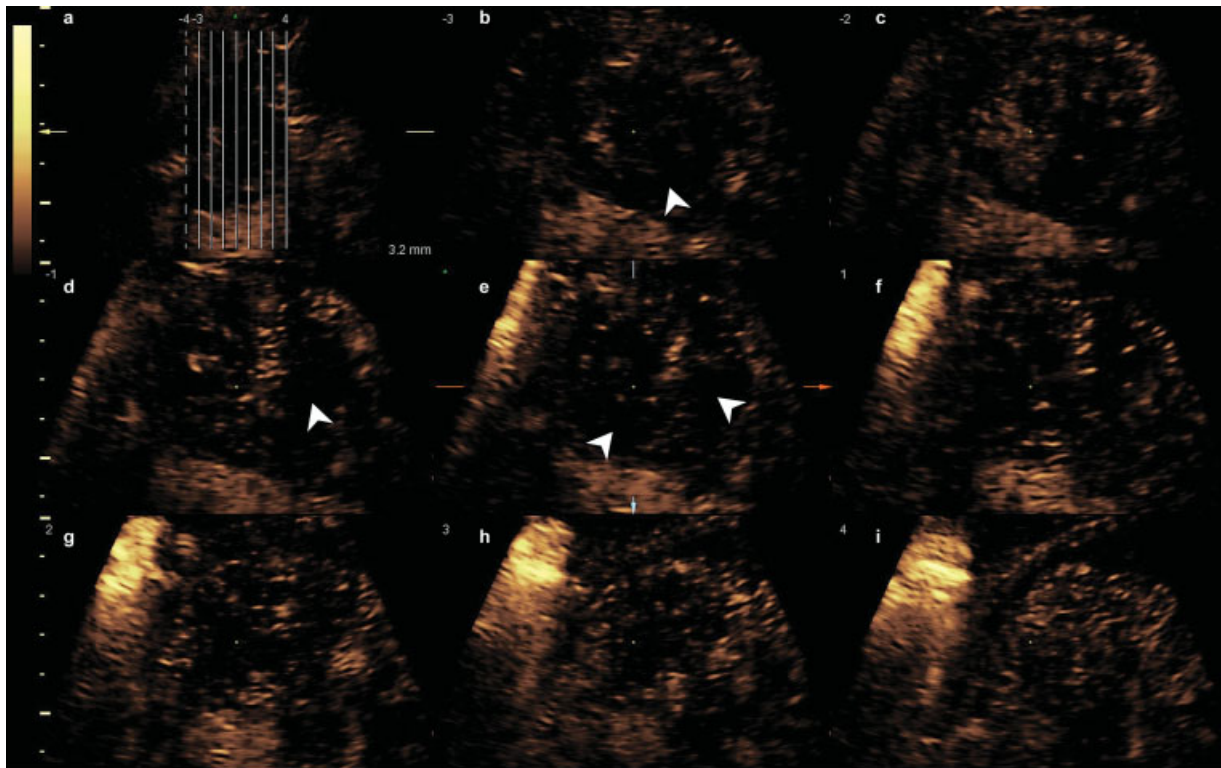


**Fig. 1** Multiple scans from an HCC patient managed with TACE. Pretreatment CEUS (a) shows a 2.3 cm enhancing mass (arrow) in segment 6. The mass is also visualized on contrast-enhanced T1-weighted axial MRI (b), and intra-operative arteriogram (c). The tumor showed no enhancement (arrows) on the 2-week (d) and 4-week (e) postembolization CEUS, indicating tumor avascularity. The 4-week post-treatment contrast-enhanced T1-weighted axial MRI (f) confirmed these findings. Reproduced with permission from Shaw et al.<sup>31</sup>

reference standard at one month. Additionally, the inter-reader agreement for 3D CEUS was excellent (kappa value = 0.83). Another study compared the performance of 3D CEUS at 1 day post-treatment with CECT at 1 month post-RFA of hepatocellular carcinoma (HCC). The study used Sonazoid as the ultrasound contrast agent and reported an excellent diagnostic performance by 3D CEUS with a sensitivity, speci-

ficity, and accuracy of 97%, 100%, and 97% respectively.<sup>53</sup> Similar performance was reported in a study that included other LRTs but used MRI as a standard of reference.<sup>54</sup> **Fig. 2** illustrates a 3D CEUS scan of HCC after TARE. Despite the aforementioned results, the added benefit of static 3D CEUS compared with 2D CEUS in assessing tumor treatment response is still in question.<sup>54,55</sup>



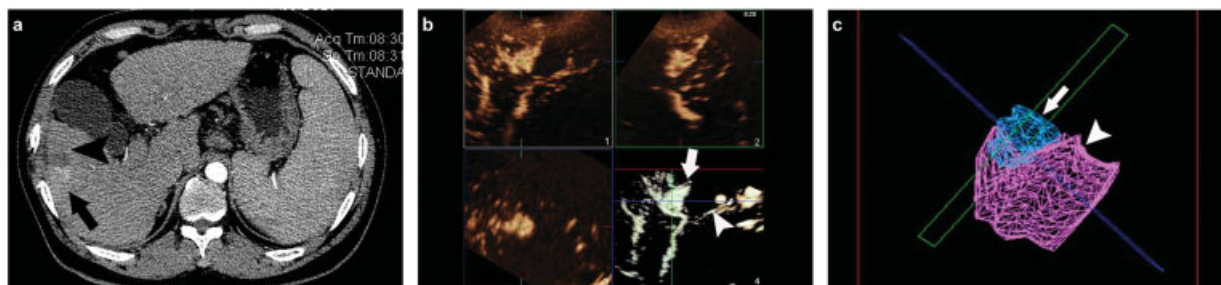


**Fig. 2** 3D CEUS of an HCC 6 months after TARE. The top left panel (a) depicts a sagittal view of the tumor and slices placement in the coronal plane. The distance between the slices was set to 3.2mm. Panels B-I show sequential sagittal slices of the tumor. Areas with minimal to no enhancement (white arrows) in most of the tumor region indicate tumor tissue necrosis. The lesion was later confirmed to be nonviable on contrast-enhanced MRI.

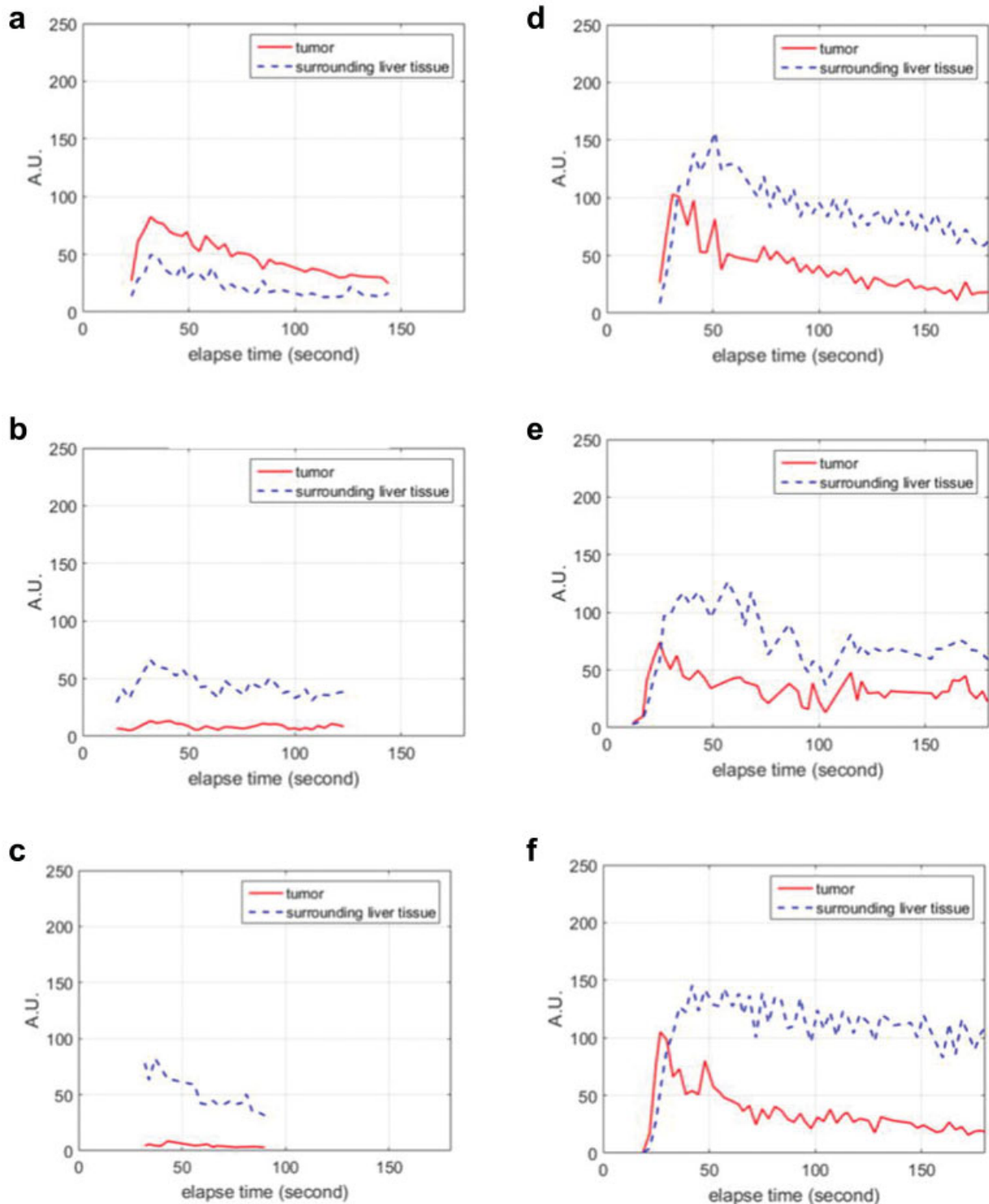
### 4D CEUS in LRT Response Monitoring

Technological advances in 2D matrix array transducers and computational image processing power now allow dynamic 3D CEUS images, also known as 4D CEUS, in near real-time. Electronic matrix transducers provide real-time or near real-time volumetric scanning which minimizes motion artifacts. This novel imaging technique combines the spatial resolution of 3D CEUS and the real-time visualization of perfusion dynamics. 4D CEUS is better than dynamic 2D CEUS in outlining the anatomic structures and their spatial relationship and may better visualize the vascularity patterns and perfusion dynamics.<sup>56</sup>

Wang et al. used 4D CEUS for HCC response assessment after ablation.<sup>57</sup> The study recruited 75 HCC patients who underwent ultrasound-guided percutaneous ablation; either thermal ablation (RFA or MWA) or chemical ablation using ethanol. The ablated tumors were examined at one month post-treatment using 4D CEUS and contrast-enhanced CT (CECT). Using CECT as the reference standard, the reported sensitivity, specificity, and diagnostic accuracy of 4D CEUS were 88.2%, 98.6%, and 96.6% respectively. An example of an incomplete ablation detected by both 4D CEUS and CECT is shown in ►Fig. 3. A similar study was performed on 42 HCC patients receiving ablation treatment. The patients were evaluated with 2D CEUS, 4D CEUS, and MRI (the standard



**Fig. 3** (a) Contrast-enhanced CT of an HCC lesion treated with radiofrequency ablation. The necrotic area is highlighted by the short black arrow, while nodular enhancement indicating viable tumor tissue (highlighted by the long black arrow). (b) 3D-CEUS showing irregular nodular enhancement (long white arrow) at the periphery of the treated region (short white arrow), corresponding to residual tumor viability. (c) 3D rendering of the treated tumor with the necrotic parts shown in pink (short white arrow) and the residual viable tumor shown in blue. Reproduced with permission from Wang et al.<sup>57</sup>

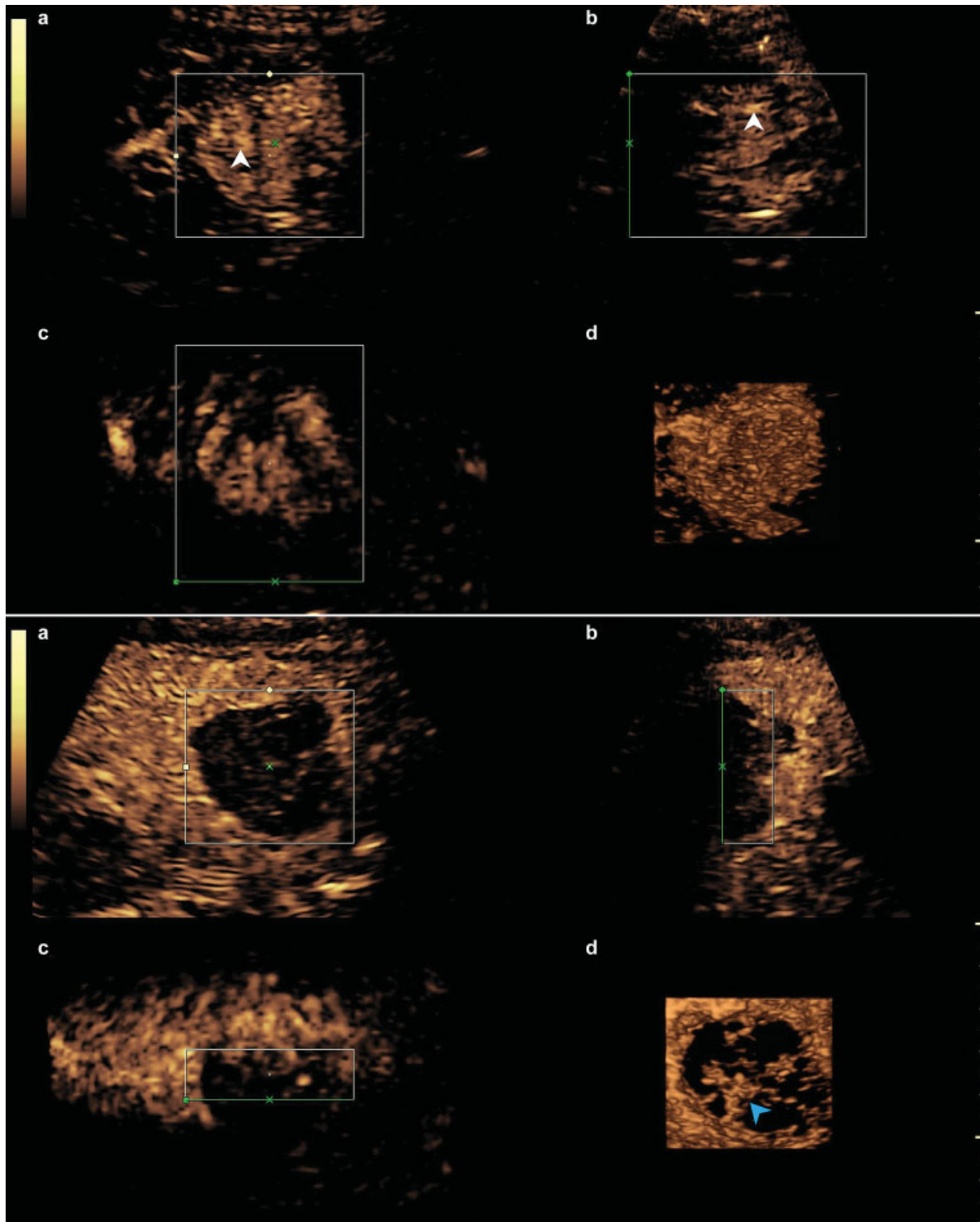


**Fig. 4** Time-intensity curves generated from 3D CEUS scans of two HCC patients treated with TACE. Time (in seconds) is plotted on the x-axis, and the signal intensity (in arbitrary units) is plotted on the y-axis. The curves on the right-hand side are for a patient with complete response to treatment: prior to TACE (a), 1–2 weeks post TACE (b), and ~1 month post TACE (c). The curves on the left-hand side are for a patient with incomplete response to treatment: prior to TACE (d), 1–2 weeks post TACE (e), and ~1 month post TACE (f). Reproduced with permission from.<sup>59</sup>

of care) exams at one month post-ablation. The combination of 2D CEUS and 4D CEUS had sensitivity of 100%, specificity of 91.7%, and diagnostic accuracy of 92.9%.<sup>58</sup>

The previously mentioned studies relied on qualitative assessment by readers to determine treatment response to HCC. Such approach is limited by the substantial variability

between readers.<sup>31</sup> On the other hand, quantitative analysis of CEUS images provide a more objective approach and may be more sensitive in early evaluation of treatment response. Time-intensity curves (TIC) produce a set of parameters that can be employed as predictors of treatment response. In a study by Nam et al., quantitative 4D CEUS was investigated as

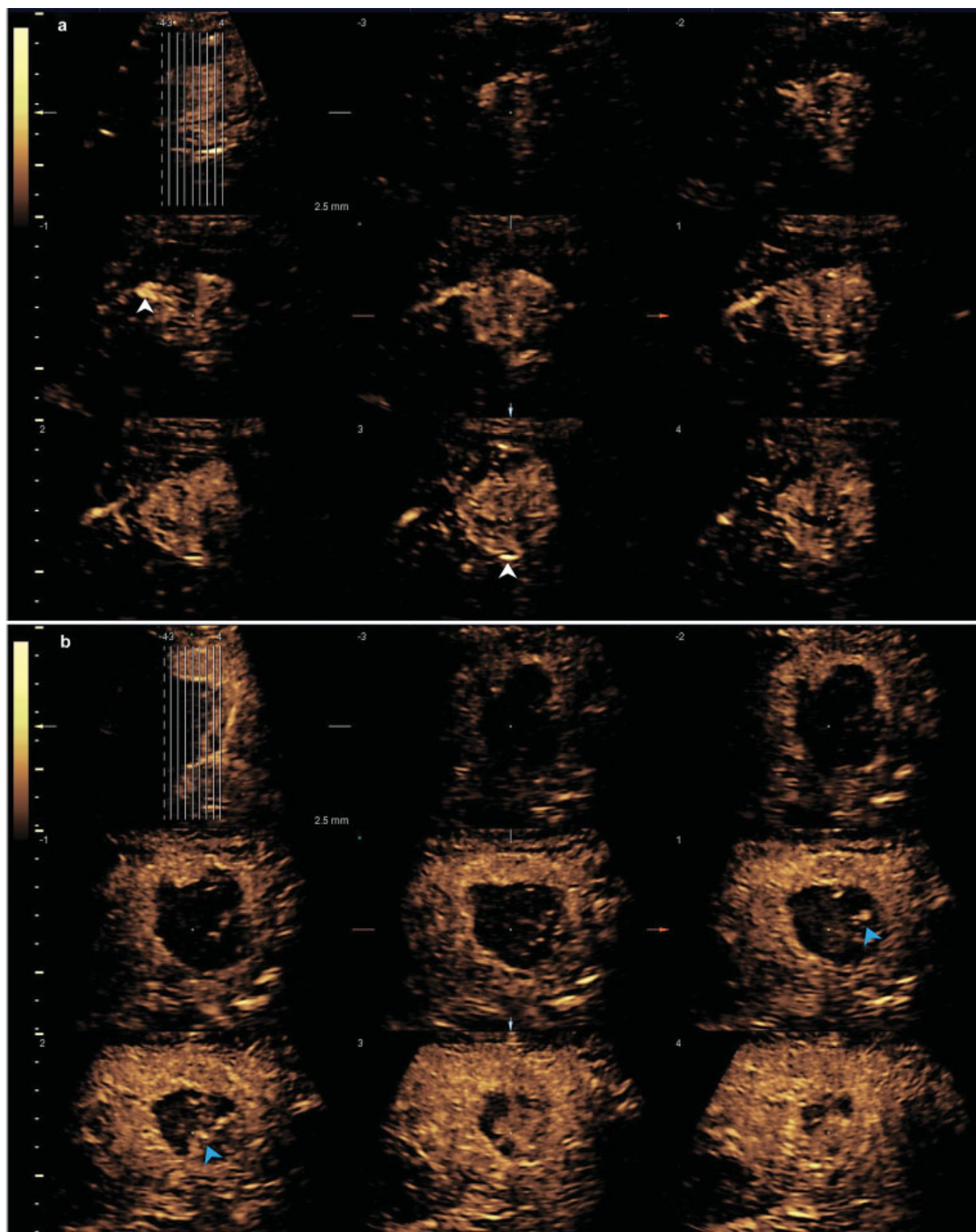


**Fig. 5** Volumetric CEUS of HCC treated with TACE in three planes: sagittal (a), coronal (b), and axial (c). The top panel shows the pre-treatment scan, where hyperenhancement can be noted in the tumor region (white arrows), a hallmark of HCC. The bottom panel shows the tumor one-week post-treatment. Residual nodular enhancement can be seen at the periphery of the lesion (blue arrow) indicating viable tumor. Residual tumor was later confirmed on contrast-enhanced MRI one month after TACE and retreated with thermal ablation two months after TACE.

a method to identify the outcome of TACE treatment early after the procedure.<sup>59</sup> The subjects were scanned by 2D and 4D CEUS 2 weeks before TACE, 1–2 weeks after TACE, and one month after TACE. The treatment response reference standard was CECT or MRI at 4–6 months post TACE or angiogra-

phy if earlier retreatment was required. After TIC analysis, peak intensity values on 3D CEUS were significantly lower in the complete response group than the incomplete response group at 1–2 weeks post TACE and one month post TACE. An example of this work is depicted in ►Fig. 4. Additionally,





**Fig. 6** A multi-slice view of volumetric CEUS of the same tumor depicted in **figure (5)**. The top panel shows the tumor pre-treatment with hyper-enhancing area (white arrows). The bottom panel shows the tumor one week after TACE, where residual nodular enhancement is observed at the periphery of the lesion (blue arrows). The distance between the shown slices is 2.5 mm. This viewing mode is expected to aid in interpretation by providing a thorough review of slices through the volume.

residual tumor estimates by 4D CEUS were highly concordant with the MRI estimates ( $r=0.94$ ), 2D CEUS had lower concordance rates with MRI ( $r=0.73$ ). These findings emphasize the capability of 4D CEUS in early evaluation of treatment

response to LRTs which allows earlier retreatments and overall improved clinical outcomes. ► **Figs. 5** and **6** show examples of volumetric 3D CEUS of an HCC before and after TACE treatment.



## Conclusion and Future Directions

CEUS techniques have been shown as a viable alternative to cross-sectional imaging modalities in tumor response assessment. CEUS not only provides similar diagnostic performance but also has many advantages such as portability, cost-effectiveness, lack of ionizing radiation, and an excellent safety profile. The clinical relevance of 4D CEUS has been growing in recent years and offers near real-time contrast imaging in three orthogonal planes overcoming spatial constraints and operator dependence of 2D CEUS. Recent implementation of volumetric analysis of 4D images enable extraction of multiple parameters from time-intensity curves and multi-parametric analysis improving the utility of 4D CEUS imaging in early identification of treatment response.<sup>60</sup>

The majority of work to date require manual regions of interest to segment the tumors. In the future, segmentation is expected to be less operator-dependent and will shift in the direction of full automation. As such, machine learning algorithms will be able to better segment the tumor region and can potentially be trained to distinguish residual tumor from necrotic tissue. This will make 4D CEUS more reproducible and reliable in detection of residual or recurrent disease.

### Conflict of Interest

None.

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