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Evaluation of Hepatocellular Carcinoma Transarterial Chemoembolization using Quantitative Analysis of 2D and 3D Real-time Contrast Enhanced Ultrasound

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Abstract

Quantitative 2D and 3D contrast-enhanced ultrasound (CEUS) was assessed to evaluate early transarterial chemoembolization (TACE) treatment response. Seventeen patients scheduled for TACE for the treatment of hepatocellular carcinoma participated in the study. 2D and 3D CEUS were performed for each patient at three time points: prior to TACE, 1–2 weeks post TACE, and 1 month post TACE. Peak-intensities of the tumor and surrounding liver tissue were calculated from 2D and 3D data before and after TACE and used to evaluate tumor treatment response. Residual tumor percentages were calculated from 2D and 3D CEUS acquired 1–2 weeks and 1 month post TACE and compared with results from MRI 1 month post TACE. Nine subjects had complete response while 8 had incomplete response. Peak-intensities of the tumor from 3D CEUS prior to TACE were similar between the complete and incomplete treatment groups ($p=0.70$), while 1–2 weeks ($p<0.01$) and 1 month post treatment ($p<0.01$) were significantly lower in the complete treatment group than in the incomplete treatment group. For 2D CEUS, only the peak-intensity values of the tumor from1 month post TACE were significantly different ($p<0.01$). The correlation coefficients between 2D and 3D residual tumor estimates 1–2 weeks post TACE and the estimates from MRI were 0.73 and 0.94, respectively, while those from 2D and 3D CEUS 1 month post TACE were 0.66 and 0.91, respectively. Quantitative analysis on 2D and 3D CEUS shows potential to differentiate patients with complete *vs.* incomplete response to TACE as early as 1–2 weeks post treatment.

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Keywords

3D contrast enhanced ultrasound; hepatocellular carcinoma; transarterial chemoembolization; therapy response; quantitative analysis

1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and its incidence and mortality rates have been rising for the last decade (Altekruse et al 2014). The management of HCC depends on both the stage of the disease and underlying liver function (Spârchez et al 2016). Transarterial chemoembolization (TACE) is the preferred treatment for patients with intermediate Stage B who do not have symptoms, but have large, multifocal tumors without vascular invasion or metastasis beyond the liver, based on the Barcelona Clinic Liver Cancer staging system (Sciarra et al 2015). TACE may also be applied to patients waiting on liver transplantation as a bridging strategy to limit tumor growth while on the waiting list (Sciarra et al 2015).

Conventional TACE (c-TACE) is performed using intra-arterial chemotherapy mixed with ethiodol followed by embolization with gelfoam particles or other embolization materials (Burrel et al 2012). This method has limitations such as non-uniform arterial obstruction from manually prepared gelfoam and toxicity induced by the release of chemotherapy to the systemic circulation (Burrel et al 2012). A newer method, TACE with drug-eluting beads (DEB-TACE), which slowly release chemotherapy after embolization, has therefore been developed (Burrel et al 2012). The efficacy of both TACE techniques depends on complete embolization of tumor arterial supply and is determined by residual tumor enhancement on imaging post TACE, since histopathologic examination of each nodule is neither feasible nor reasonable for patients with HCCs (Spârchez et al 2016, Lammer et al 2009, Shin 2009). The objective response (complete or partial response) rate of TACE is about 15–75% of tumors (Shin 2009, Marelli et al 2007) and incomplete response to TACE requires repeated TACE or alternative treatments (Takayasu et al 2006).

Contrast-enhanced computed tomography (CE-CT) and contrast-enhanced magnetic resonance imaging (CE-MRI) are widely used for the assessment of TACE response (Shaw et al 2015, Brown et al 2012). The Society of Interventional Radiology guidelines recommend delaying follow-up imaging by 4–6 weeks post TACE (Brown et al 2012, Kloeckner et al 2010). This time-point for imaging follow-up was suggested due to low specificity of both CT and MRI imaging in differentiating peripheral viable tumor from peritumoral inflammatory response and also to minimize the amount of imaging artifact from intraparenchymal ethiodol on CE-CT (Brown et al 2012, Yan et al 2002). However, earlier detection of TACE response could potentially improve the management of HCC (Shaw et al 2015, Kono et al 2007).

Contrast-enhanced ultrasound (CEUS) has been evaluated in several studies as an early indicator for TACE efficacy (Shaw et al 2015, Kono et al 2007, Cho et al 2015). Recently, CEUS for liver imaging was approved by the United States Food and Drug Administration and it has been used as a primary imaging modality for many hepatic applications worldwide

(Claudon et al 2013). As a modality, CEUS has additional benefits such as availability, portability, cost, no nephrotoxicity, and lack of ionizing radiation. The study by Salvaggio et al. showed that CEUS performed 1 month post TACE detected all incomplete responses in 38 HCCs using angiography as reference standard (Salvaggio et al 2010). Cho et al. reported that all patients with positive CEUS findings at 4 weeks (8 out of 12 TACE patients) showed positivity and residual viable HCC in MRI at 4 or 12 weeks (Cho et al 2015). Kono et al. evaluated 23 HCCs within 2 weeks and 10 HCCs within 1 month after c-TACE using CEUS (Kono et al 2007). Of these 33 tumors, there were no false-negative results and only one false-positive result occurred when the CEUS was performed within 1 day after TACE. Similar results were reported in a study with 14 DEB- TACE patients, where CEUS images at 1–2 weeks post treatment resulted in 100% accuracy (Shaw et al 2015).

While these studies demonstrated CEUS as an alternative or earlier indicator of TACE efficacy, they were limited to qualitative evaluations by CEUS experts using 2D images. The accuracy of qualitative evaluation depends largely on the reader's experience. In the study by Shaw et al., the intra- and inter-read variability with CEUS was higher than with CE-MRI or CE-CT. They explained that it was caused some readers' limited experience in CEUS relative to other modalities (Shaw et al 2015). Also, evaluating an inherently 3D tumor with 2D CEUS imaging increases user variability. Moreover, the vasculature of HCCs may be heterogeneous over the 2D imaging planes, which can affect the assessment of treatment response. Xu et al. used static 3D CEUS to evaluate the treatment response of liver cancer (n=107) after local therapies and found that 3D CEUS improved diagnostic confidence relative to 2D CEUS (Xu et al 2010). However, the 3D CEUS follow up times ranged from 10 minutes to 28 months in that study (Xu et al 2010).

A few CEUS studies of TACE have adopted quantitative analyses to better evaluate the vasculature within HCCs (Moschouris et al 2010, Uller et al 2011). Moschouris et al. calculated the percentage of necrosis within HCCs based on 2D CEUS at 2 days and 35-40 days post TACE in order to evaluate the amount of early and delayed tumor necrosis by DEB-TACE (Moschouris et al 2010). Uller et al. used time-intensity curves from 2D CEUS to evaluate the microcirculation of HCCs with intraarterial and intravenous injections of contrast agent during DEB-TACE (Uller et al 2011). However, neither the percentage of necrosis nor time-intensity curves correlated directly with therapy response. Consequently, the purpose of this study was to perform quantitative analysis on 2D and 3D CEUS to establish an earlier and accurate indicator for patients requiring retreatment post TACE.

2. Materials and methods

2.1. Subjects

The study was approved by our institutional review board and was compliant with the Health Insurance Portability and Accountability Act. All participants in the study provided written informed consent. The ultrasound contrast agent utilized in this study was Definity (Lantheus Medical Imaging, North Billerica, MA).

Seventeen patients scheduled for TACE for the treatment of HCC participated in the study. Participants had to be medically stable and have no known hypersensitivity or allergy to

components of Definity. Patients who were pregnant or nursing or having severe cardiac complications were excluded. Demographic information was recorded.

2.2. Ultrasound Examinations

Each subject underwent 2D and 3D CEUS exams at three time points: within 2 weeks prior to TACE, 1-2 weeks post TACE, and approximately 1 month post TACE. The ultrasound exams were performed using a Logiq E9 with C1-6-D (bandwidth of 1-6 MHz with 70° field of view) and RAB-2-5-D probes (bandwidth of 1-5 MHz with 85° field of view; GE Healthcare, Wauwatosa, WI, USA). All CEUS imaging was performed using the scanner's CEUS mode implemented by the combined technology of amplitude modulation and phase inversion. After acquiring baseline images, subjects received a bolus injection of 0.2-0.3 ml of Definity intravenously, followed by a 10 ml saline flush for 2D CEUS examination. 2D CEUS imaging was performed using a dual-imaging mode, which enabled side by side visualization of B-mode and CEUS. Following 2D CEUS examination, subjects waited 10 minutes for the clearance of the contrast agent before 3D baseline imaging was performed. Then, subjects received an identical bolus injection of Definity for a 3D CEUS examination. In both of 2D and 3D CEUS, data was collected continuously from the entire tumor and surrounding tissue from the arrival of the contrast into the liver until wash-out of the agent was observed. Imaging was performed in CEUS mode at low mechanical index below 0.11. The frame and volume rate for 2D and 3D CEUS were 8-9 frames/second and 0.3-0.4 volume/second, respectively. All data were stored for offline analysis.

2.3. Time-intensity curve analysis

For 2D CEUS, a region of interest (ROI) was drawn for both the HCC and the surrounding liver tissue on 2D CEUS images. A time-intensity curve was obtained from the area of the tumor and the surrounding liver tissues by calculating the mean intensities of the corresponding ROI over time. To obtain a time-intensity curve from 3D CEUS, the collected 3D volume at each time point was analyzed as 8 equidistant 2D slices across the tumor using 4D View (GE Healthcare, Zipf, Austria). On each 2D CEUS slice, a ROI was drawn for the tumor and for the surrounding liver tissue. An example of the ROI selection for 3D CEUS is presented in the figure 1. The mean intensities of the volume of tumor and surrounding liver tissues were calculated by averaging the intensities within the corresponding ROIs over the eight 2D slices using Matlab R2015b (Mathworks, Natick, MA, USA). The same process was repeated for all 3D CEUS data at different time points.

2.4. Residual tumor quantification

For the quantification of residual tumor in 2D or 3D CEUS, images or volumes showing the peak-intensity were selected based on time-intensity curve analysis described above. The residual tumors were quantified using the equation below:

$$\textit{Residual tumor}\,(\%) = 100 - \frac{\textit{Non} - \textit{enhancing intratumoral volumn or area}}{\textit{Total tumor volumn or area}} \times 100$$

For the 3D quantification, the total tumor and non-enhancing intratumoral volumes were calculated by adding 15 equidistant 2D areas across the tumor extracted from B-mode

volume and CEUS volume, respectively. In 2D, the residual tumor percentage was obtained by comparing tumor area on the B-mode image and non-enhanced area on the CEUS image. The CEUS volume (i.e. enhanced volume) and non-enhanced area on the CEUS images were identified visually.

2.5. Evaluation of TACE response

The TACE response was evaluated based on CE-MRI/CT obtained one month or six months post-TACE and assessed by a radiologist blinded to the results from the CEUS exams. Complete response was defined as no enhancement shown in 6 month MRI. Incomplete response was defined when 1) residual tumor enhancement was seen at MRI 1 month post TACE and confirmed on angiography during subsequent retreatment or 2) tumor growth or residual enhancement was reported at 6 month follow up. In patients with incomplete treatment response, the percentage of residual tumor was quantified in 10% increments based on MRI acquired at 1 month post TACE by a radiologist blinded to the ultrasound results. The MRI evaluation was performed based on multiple slices over the whole tumor volume.

2.6. Statistical analysis

The peak-intensities from the tumor and surrounding liver tissues were grouped by TACE response. A Wilcoxon rank sum test was performed to compare complete and incomplete responses with a 5% significance level using Matlab. In subjects with incomplete response, correlation coefficients (r) were calculated between the residual tumor estimate from MRI acquired at 1 month post TACE and the residual tumor estimates from CEUS exams 1-2 weeks or 1 month post TACE. Also, Bland-Altman plots with repeatability coefficient were obtained to assess the agreements.

3. Results

A total of 17 subjects' data were included in this study (figure 2). Twelve subjects completed all 3 exams, while 5 subjects completed 2 exams (one completed exams 1 and 2, two completed exams 1 and 3, and two completed exams 2 and 3). Among the 17 subjects, 9 subjects had complete treatment response and 8 subjects had incomplete treatment response. The subjects included 14 males and 3 females. The mean age of the subjects was 64 years and the range was 54-78 years. The subjects' body mass index, tumor size, tumor location, and received treatment are summarized in Table 1.

Overall, the HCCs after TACE were observed as hypo-echoic on CEUS 2 weeks and 1 month post TACE. However, there was one case showing CEUS artifacts and this is presented in figure 3. The subject was treated with DEB-TACE and the beads were shown hyperechoic on CEUS 2 weeks post treatment. These artifacts disappeared on CEUS 1 month post TACE.

3.1. Time-intensity curve analysis

The examples of time-intensity curves are shown in figure 4. Prior to TACE, the peak-intensity values of the tumor on 3D CEUS were similar between the complete and

incomplete response groups (90.2 ± 33.4 (mean ± standard deviation) arbitrary unit (AU) vs. 98.4 ± 46.0 AU; p=0.70) but those from 1-2 weeks (30.0 ± 15.6 AU vs. 66.4 ± 25.4 AU; p<0.01) and 1 month post TACE (23.6 ± 13.5 AU vs. 81.8 ± 36.0 AU; p<0.01) were significantly lower in the complete response group compared to the incomplete response group. These results are summarized in Table 2. The peak-intensity values of the surrounding liver tissue region obtained from 3D CEUS did not show differences between the complete and incomplete response groups in any case (p>0.12). However, the ratios of the tumor peak-intensity to surrounding liver tissue peak-intensity showed the same results as the peak-intensity values of tumor regions (Table 2). The ratios of the peak-intensity value of tumor to that of surrounding liver tissue regions from 3D CEUS 1-2 weeks and 1 month post TACE demonstrated an ability to differentiate complete response from incomplete responses (p<0.01 for both cases).

In 2D CEUS, peak-intensity values of the tumor region prior to TACE and 1-2 weeks post TACE did not show differences between the complete and incomplete response groups (p>0.1; Table 2), while those from the data 1 month post TACE were significantly lower in complete response group compared to incomplete response group (p<0.01). Similar to the findings from 3D CEUS, peak-intensity values from the surrounding liver tissue did not show differences between complete and incomplete response groups (p>0.06; Table 2). The ratios of the tumor peak-intensity to surrounding liver tissue peak-intensity showed the same results as the peak-intensity values of tumor regions (Table 2). The peak-intensity results from 2D and 3D CEUS 2 weeks and 1 month post TACE are compared in figure 5. Overall, the peak-intensities from 2D and 3D CEUS were not significantly different (p=0.64).

3.2. Residual tumor quantification

For the subjects with complete response, 2D and 3D CEUS 2 weeks post TACE resulted in 1 and 2 false positive cases (1 case overlapped), respectively. In case of 2D and 3D 1 month post TACE, there were 2 and 3 false-positive cases (1 case overlapped), respectively. Among the subjects with incomplete response, there was one subject whose 1 month MRI was evaluated as complete response but 6 month follow-up MRI showed a recurrent tumor and determined to have incomplete response. For this case, the 2D and 3D CEUS showed consistent enhancement within the tumor at both 2 weeks and 1 month post TACE. There was no false-negative case in all CEUS evaluations.

The residual tumor estimates from MRI evaluations 1 month post TACE ranged from 0% to 90% with a mean value of 38% for the subjects with incomplete response. Those from 2D and 3D CEUS 1-2 weeks post TACE ranged from 10 to 80% with a mean value of 46% and from 20 to 80% with a median value of 37%, respectively. The residual tumor estimates from 2D and 3D CEUS 1 month post TACE were 30-80% with a mean value of 51% and 20-100% with a mean value of 44%, respectively. Figure 6 shows an example of calculating tumor size and non-enhanced tumor size using 2D or 3D B-mode and CEUS data acquired 1-2 weeks post TACE. The case presented in figure 5 had incomplete TACE response and a residual tumor estimate from MRI 1 month post TACE of 20%, while the residual tumor estimates from 2D and 3D CEUS 1-2 weeks post TACE were 10% and 20%, respectively. The correlation coefficients between 2D and 3D residual tumor estimates 1-2 weeks post

TACE and the estimates from MRI 1 month post TACE were 0.73 and 0.94, respectively, while those from 2D and 3D CEUS 1 month post TACE were 0.66 and 0.91, respectively (figure 7). The Bland-Altman plots with repeatability coefficients are presented in figure 8.

4. Discussion

Currently, CE-CT and CE-MRI are widely used for imaging evaluation after TACE and the Society of Interventional Radiology guidelines recommend follow-up CE-CT or CE-MRI 4-6 weeks post TACE (Brown et al 2012, Kloeckner et al 2010). A lack of enhancement indicates a lack of residual tumoral blood flow, due to complete embolization and tumor necrosis. The 4-6 week time point has been suggested based on experience with the use of Lipiodol and CE-CT; the non-tumor bearing liver requires 3-4 weeks to eliminate Lipiodol by Kupffer cell phagocytosis (Brown et al 2012). In CE-MRI, the use of low molecular weight and water soluble contrast agents renders it difficult to differentiate granulation tissue and residual tumor perfusion and to differentiate peripheral viable tumors from inflammatory peritumoral infiltration after TACE (Yan et al 2002). Differentiation between viable tumor and inflammation can be made in some cases by evaluating enhancement washout kinetics. Nevertheless, the cost of imaging and difficulty associated with inflammation in many cases has resulted in follow-up imaging recommendation remaining at 4-6 weeks (Brown et al 2012). Thus, CEUS has been assessed as an earlier follow-up imaging tool for TACE and showed potential to be effective as early as 1-2 weeks (Shaw et al 2015, Cho et al 2015). While those studies (Shaw et al 2015, Cho et al 2015) evaluated TACE response using a qualitative measure, our results showed that peak-intensity, a quantitative measure, could be used to predict TACE response as early as 1-2 weeks. Moreover, the residual tumor estimates from 2D CEUS 1-2 weeks were correlated well with that from MRI 1 month post TACE (r=0.73) and this correlation improved with the use of 3D CEUS (r=0.94).

The most common quantitative assessment of therapy response is tumor size change and is included in the World Health Organization criteria and Response Evaluation Criteria in Solid Tumors (RECIST; Gonzalez-Guindalini et al 2013). However, the bi-dimenstional (Miller et al 1981) or uni-dimensional (Therasse et al 2000) measurement of the whole treated tumor may not properly reflect therapy response because treatment induced tumor necrosis does not cause immediate shrinkage of tumor in parallel (Italian Association for the Study of the Liver et al 2013). Thus, the modified RECIST (mRECIST) chose a measurement of viable (contrast-enhanced) tumor instead of whole treated tumor though it still recommends the use of the longest viable tumor diameter (Lencioni and Llovet 2010). In the study of correlating imaging evaluation on CT with pathologic results after TACE, mRECIST underestimated and overestimated response in 10.7% and 21.9% of 178 patients, respectively, despite an overall acceptable agreement of 67.4% (Bargellini et al 2013).

Previously, the curve fitting and blood flow kinetic modeling was suggested to monitor tumor therapy (primarily anti-angiogenic therapies) serially in the same patients focusing on partial reduction in vascularity (Doury et al 2017). In this study, the coherent estimation of relative parameters was observed from the modeling. While TACE effectiveness is also evaluated based on blood flow, the result is binary and determined by complete lack of

residual flow. Hence, modeling of this reduction (in which no blood flow is ideally present) was not applied in this study.

In this study, the time-intensity curves and residual tumor estimates were obtained from 2D as well as 3D CEUS. Interestingly, the peak-intensity of tumor from 3D CEUS differentiated the complete response group from the incomplete response group 1-2 weeks and a month post TACE, while that from 2D CEUS only did 1 month post TACE. A similar finding was demonstrated when correlating residual tumor estimates from 2D and 3D CEUS to those from MRI; with 3D estimates showing a better correlation. This could be caused by the heterogeneities of TACE response and vascularity within HCCs, which 3D evaluations may be better able to reflect (cf. figure 6C). This also could explain why there were more false-positive cases in 2D CEUS than 3D CEUS in the residual tumor quantification. As expected, the peak-intensities of subjects with complete response were much lower than those of subjects with incomplete response in this study but they were not completely zero (cf. Table 2). This could have been caused by the hyperechoic artifacts by drug-eluting beads presented in figure 3A. Also the completely treated HCCs were hypoechoic but not anechoic as seen in figure 3B. Another cause was the use of circular ROI for all tumors including irregular shaped ones. The circular ROI could have contained some of surrounding liver tissue. Finally, there were false-positive cases in this study.

Time-intensity curve analysis from CEUS has been used to detect the microvessel density in HCCs (Wang et al 2007, Yang et al 2013). In one particular study, there was a significant correlation ($r=0.89$; $p<0.05$) between peak intensity and microvessel density in the study of 50 HCC patients (Wang et al 2007). The area under the curve was significantly different ($p<0.05$) between vascular endothelial factor positive and negative groups in a study with 73 HCC patients (Yang et al 2013). Also, the change in peak value, area under the curve, and slope of contrast wash-in between prior to treatment and 15 days post treatment differentiated the complete response group from the incomplete response group to the treatment of Sorafenib, which blocks tumor angiogenesis in advanced HCCs, in a study with 28 HCC patients (Zocco et al 2013). These studies (Wang et al 2007, Yang et al 2013, Zocco et al 2013) have demonstrated that parameters from time-intensity curve analysis can detect changes in vascularity within HCCs and support the results from this study that the effective embolization by TACE was reflected in the time intensity curve.

This study had some limitations. In time-intensity curve analysis (2D as well as 3D) the same ROIs were maintained throughout the analysis excluding issues arising from subjects' breathing motion. Thus, the time-resolution of time-intensity curve varied among patients. Also, the depths of the HCC and the corresponding surrounding liver tissues were not always the same, due to difficulties in some scanning windows and the subsequent attenuation difference was not accounted for. Only individual parameters were investigated at this time, due to the limited data set. In the future, multi-parametric analysis should be investigated as these approaches have been shown to improve differentiation in dynamic CEUS applications (Postema et al 2015, Wildeboer et al 2017). Finally, while a free-form of ROI was used in the residual tumor estimation, a circular-shaped ROI was used for time-intensity curve analysis, which may generate errors in segmenting tumor from peripheral tissue. Future efforts will focus on auto-segmentation algorithms to alleviate this issue.

5. Conclusions

The peak-intensity of time-intensity curves from 3D CEUS shows the potential to evaluate HCC TACE response as early as 1-2 weeks post treatment; albeit based on a limited sample size. Also, residual tumor estimates of HCCs from 2D and 3D CEUS 1-2 weeks and 1 month post TACE matched well with estimates from MRI 1 month post TACE, with 3D CEUS showing the best correlation of the two CEUS techniques.

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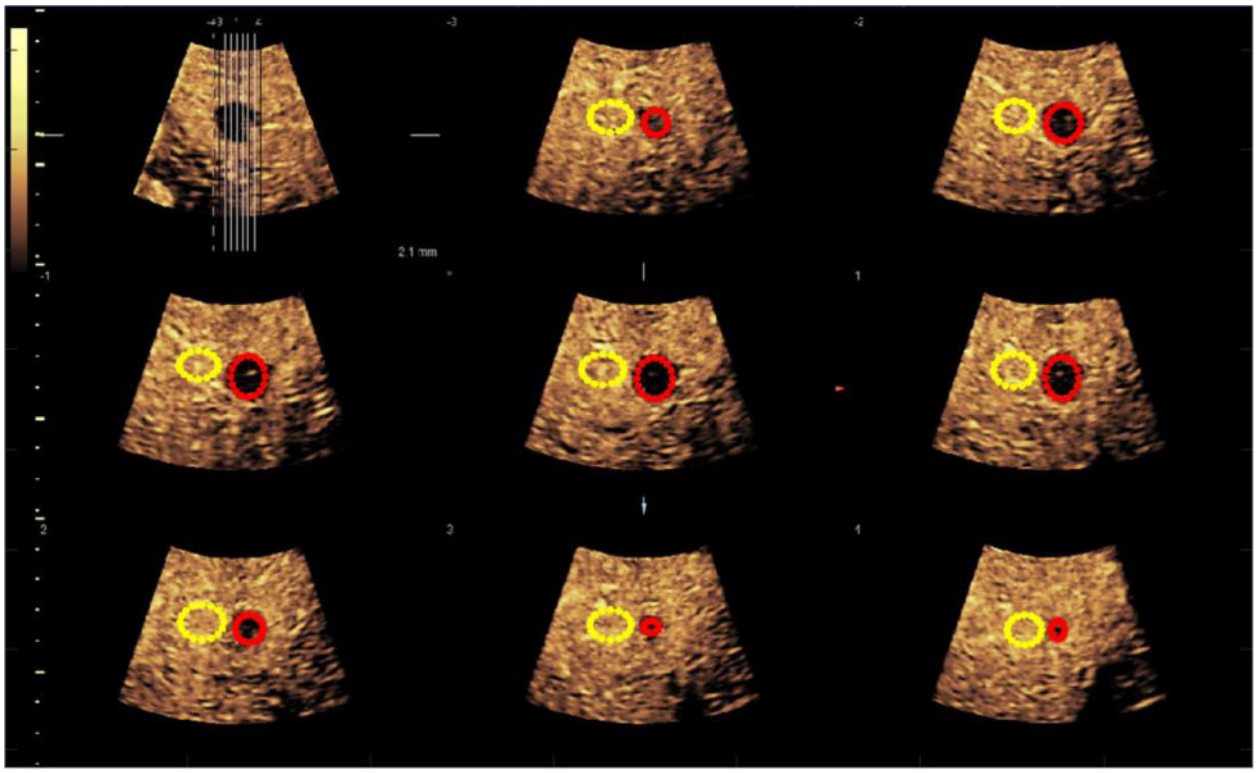

Figure 1.

An example of region of interest selections on 8 equidistant 2D slices extracted from 3D contrast-enhanced ultrasound imaging is shown. The yellow circle includes surrounding liver tissue and the red circle includes the tumor on each 2D slice.

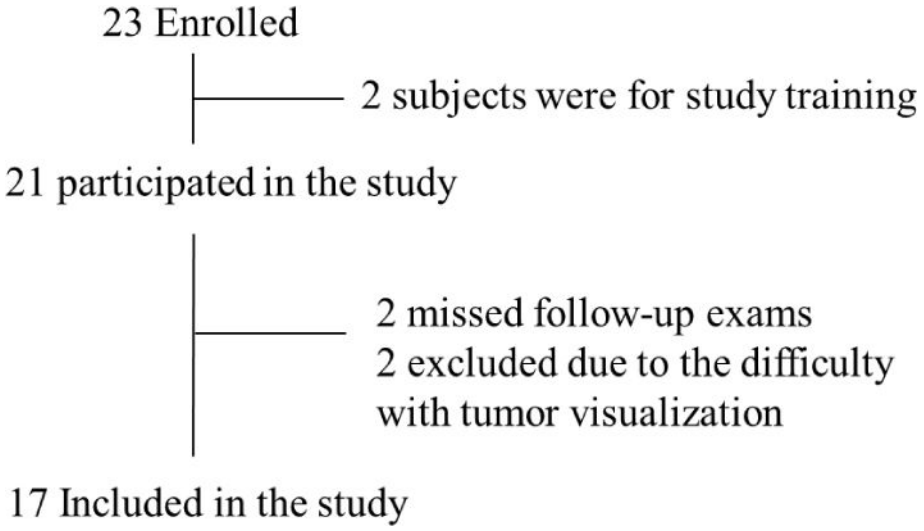

Figure 2.
Flowchart of study participants

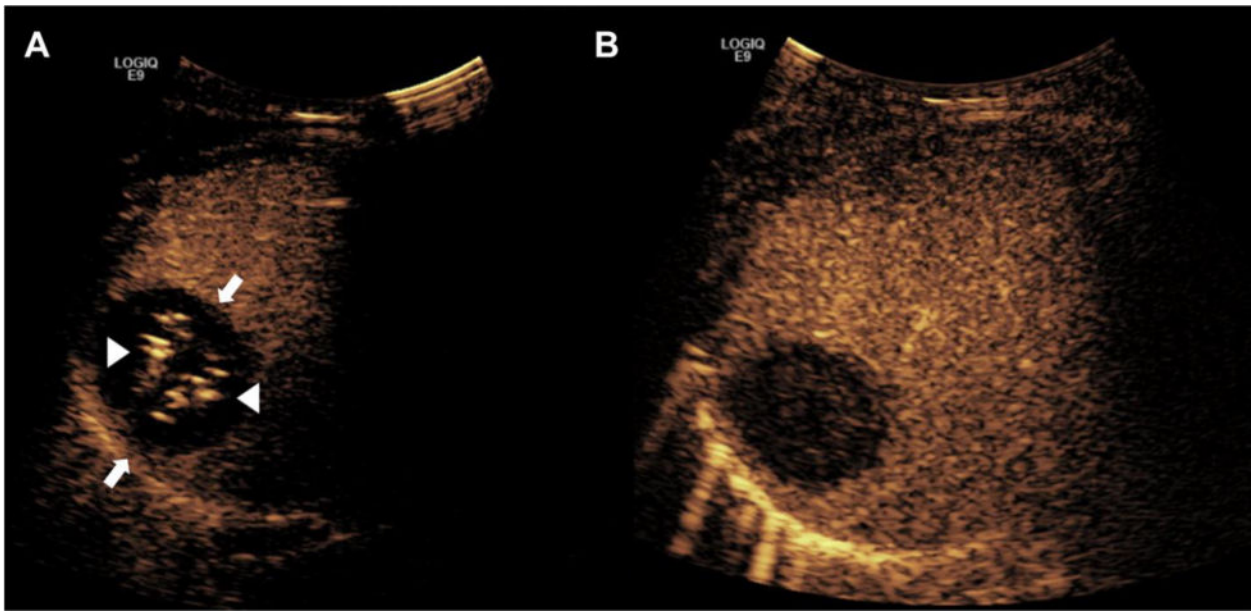

Figure 3.

(A) The contrast-enhanced ultrasound imaging 2 week post transarterial chemotherapy with drug-eluting beads showed the hyperechoic artifacts (arrowheads) within the tumor (arrows) and (B) these artifacts disappeared on contrast-enhanced ultrasound imaging 1 month post treatment.

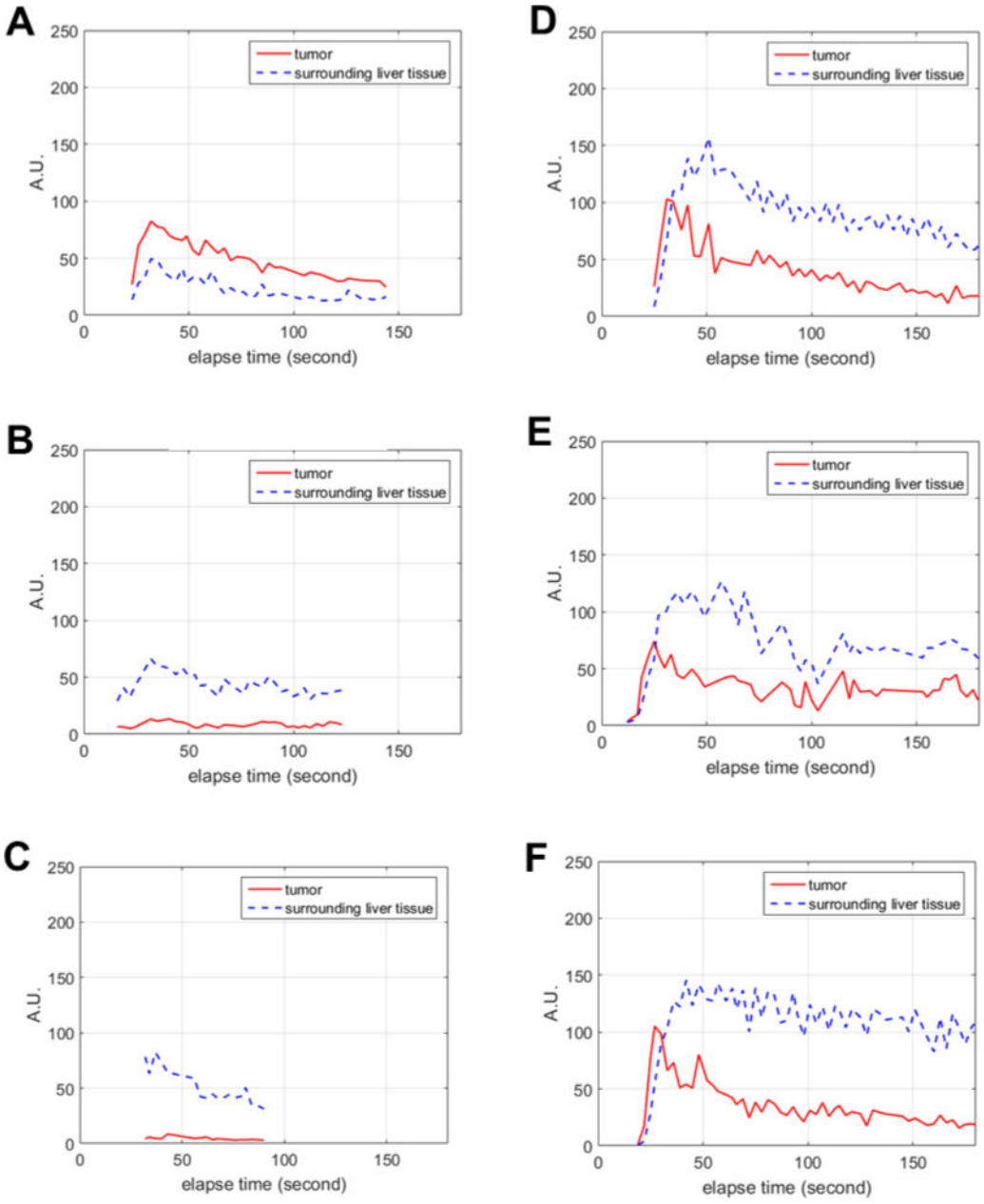

Figure 4.

These examples of time-intensity curves were acquired from a subject with complete response prior to TACE (A),1-2 weeks post TACE (B), and approximately 1 month post TACE (C) as well as from a subject with incomplete response prior to TACE (D),1-2 weeks post TACE (E), and approximately 1 month post TACE (F) using 3D CEUS (A.U: Arbitrary Unit). The peak-intensity was obtained directly from each curve.

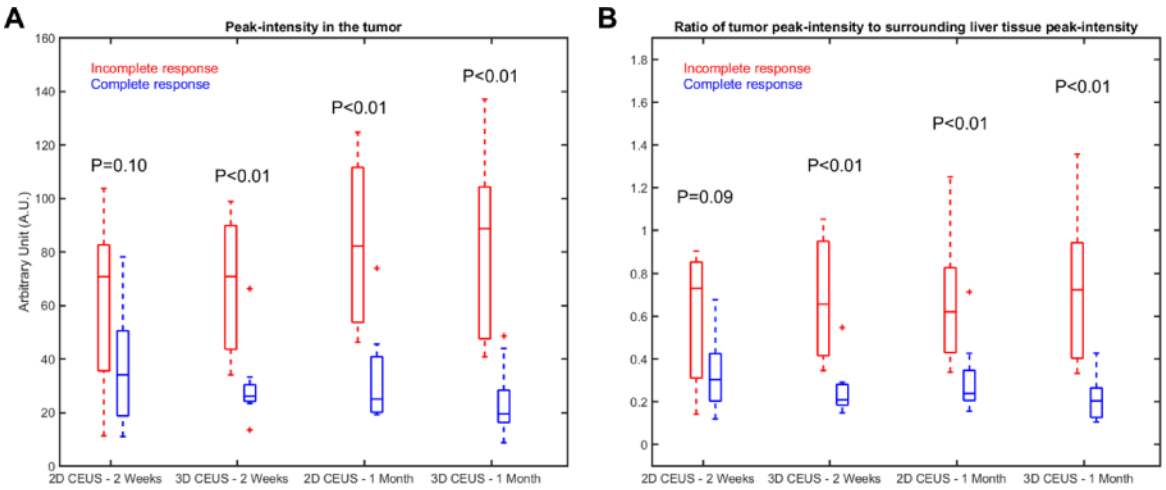

Figure 5.

The peak-intensities from 2D and 3D contrast-enhanced ultrasound 2 weeks and 1 month post transarterial chemotherapy were compared between the complete and incomplete response groups. (A) The peak-intensities in the tumor and (B) the ratios of the tumor peak-intensity to surrounding liver tissue peak-intensity showed similar performance to predict transarterial chemotherapy response in 3D contrast-enhanced ultrasound. (The central mark on each box is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extended to approximately ±2.7 standard deviation, and outliers are plotted individually).

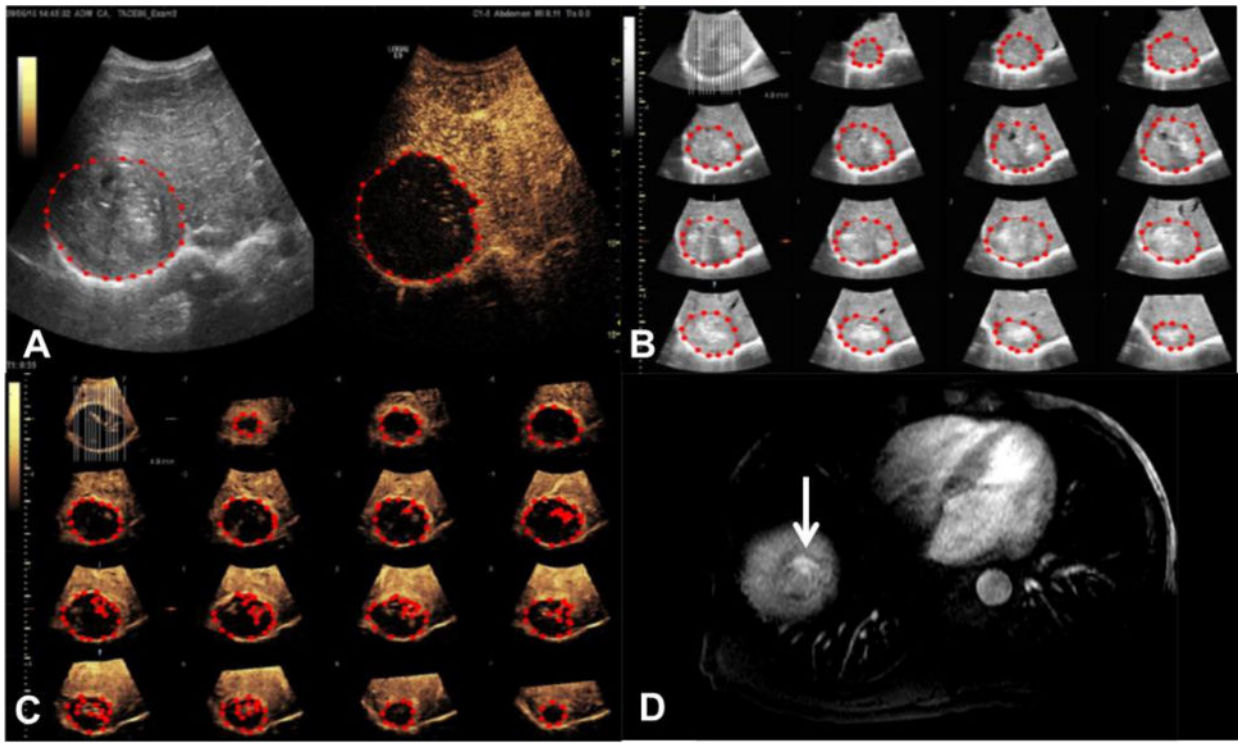

Figure 6.

An example of residual tumor estimation – (A) 2D residual tumor estimate was calculated using the difference in tumor area on B-mode and non-enhanced intratumoral area on contrast-enhanced ultrasound, each outlined in red dashed line. 3D residual tumor estimate was calculated using the differences in tumor and non-enhancing intratumoral volumes, by adding 15 equidistant 2D areas across the tumor as outlined in red dashed lines, extracted from (B) B-mode volume and (C) contrast-enhanced ultrasound volume, respectively. (D) The residual tumor (arrow) was confirmed in magnetic resonance imaging 1 month post transarterial chemotherapy.

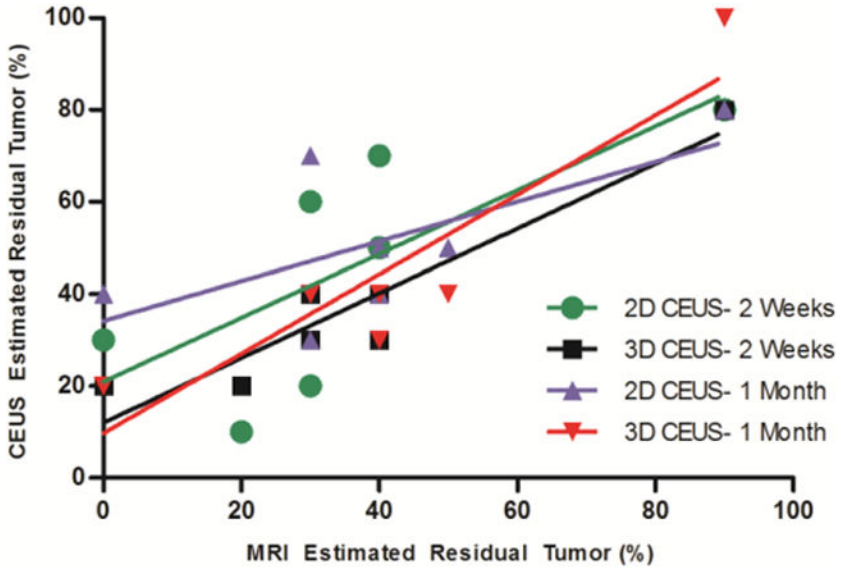

Figure 7.

The residual tumor estimates from 2D and 3D contrast-enhanced ultrasound acquired 1-2 week and 1 month post transarterial chemotherapy (TACE) were correlated with the residual tumor estimate from magnetic resonance imaging 1 month post TACE. The correlation coefficients between 2D and 3D residual tumor estimates 1-2 weeks post TACE and the estimates from magnetic resonance imaging were 0.73 and 0.94, respectively, while those from 2D and 3D contrast-enhanced ultrasound 1 month post TACE were 0.66 and 0.91, respectively.

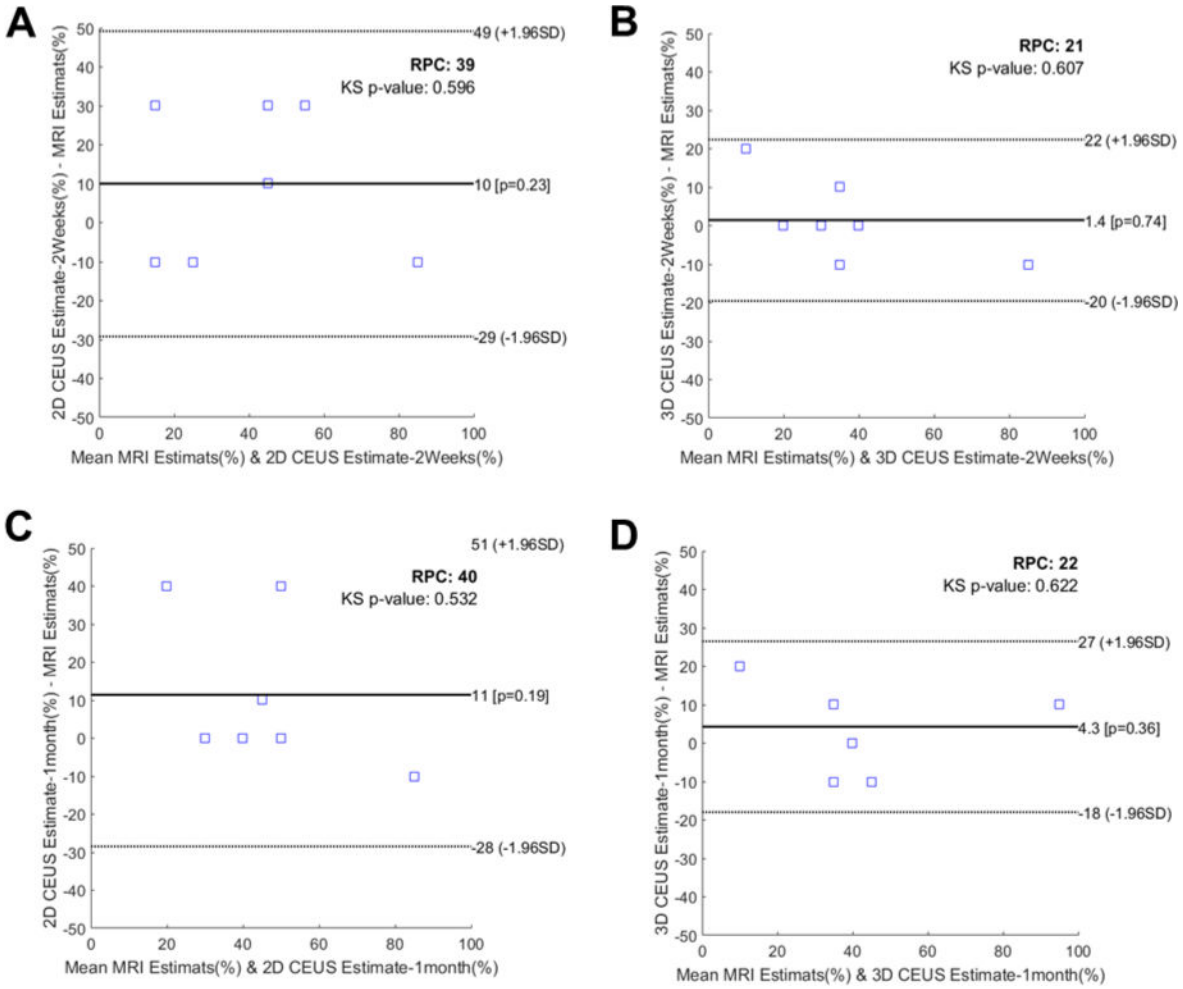

Figure 8.

The Bland-Altman plots with repeatability coefficients (RPCs) were obtained between the residual tumor estimate from magnetic resonance imaging 1 month post TACE and (A) 2D and (B) 3D residual tumor estimates 1-2 weeks post TACE as well as those from (C) 2D and (D) 3D contrast-enhanced ultrasound 1 month post TACE (KS: Kolmogorov-Smirnov test, SD: Standard deviation).

Table 1

Subjects' characteristics: sex, body mass index (BMI), age, tumor dimension, tumor location, received treatment, and transarterial chemoembolization (TACE) response results for the subjects. (c-TACE: conventional TACE, DEB-TACE: TACE with drug-eluting beads)

Subject number	Sex	BMI	Age	Tumor dimension (cm)	Tumor location	Received treatment	TACE response
1	M	35.3	63	2.5 × 2.1	Segment 6	c-TACE	Complete
2	M	22.2	71	7.8 × 8.7	Segment 7	c-TACE	Incomplete
3	M	21	55	4.2 × 3.9	Segment 8	DEB-TACE	Complete
4	M	41	54	3.7 × 1.5	Segment 8	c-TACE	Complete
5	F	32.6	78	4.1 × 3.5	Segment 6	c-TACE	Incomplete
6	M	28.7	62	2.0 × 2.3	Segment 6	c-TACE	Complete
7	M	36.5	63	2.4 × 2.3	Segment 8	c-TACE	Complete
8	M	21.9	65	5.1 × 4.5	Segment 5	c-TACE	Incomplete
9	M	21.9	68	2.1 × 2.3	Segment 7	c-TACE	Complete
10	M	29.5	62	3.2 × 2.7	Segment 6	c-TACE	Complete
11	M	40.2	62	5.5 × 4.5	Segment 4A	DEB-TACE	Incomplete
12	M	22.4	69	4.5 × 3.8	Segment 4B	c-TACE	Incomplete
13	M	31.2	69	6.6 × 5.6	Segment 2	DEB-TACE	Complete
14	F	37	65	3.6 × 2.6	Segment 4B	DEB-TACE	Complete
15	M	25	68	2.2 × 1.9	Segment 5	DEB-TACE	Complete
16	M	36	58	2.8 × 2.4	Segment 5	DEB-TACE	Incomplete
17	F	32	62	3.3 × 2.7	Segment 8	DEB-TACE	Incomplete

Table 2

The peak-intensities from time-intensity curve analysis between the complete and incomplete response groups are compared. The ratios of the tumor peak-intensity to surrounding liver tissue peak-intensity are also compared. (TACE: transarterial chemoembolization; complete response group vs. incomplete response group; mean ± standard deviation; unit: arbitrary unit)

	3D Contrast-enhanced ultrasound			2D Contrast-enhanced ultrasound		
	Prior to TACE	**1–2 weeks post TACE**	**1 month post TACE**	**Prior to TACE**	**1–2 weeks post TACE**	**1 month post TACE**
Tumor (Complete vs. Incomplete)	90.2 ± 33.4 vs. 98.4 ± 46.0 (p=0.70)	30.0 ± 15.6 vs. 66.4 ± 25.4 (p<0.01*)	23.6 ± 13.5 vs. 81.8 ± 36.0 (p<0.01*)	80.7 ± 22.4 vs. 98.4 ± 39.7 (p=0.40)	36.9 ± 23.1 vs. 62.7 ± 32.9 (p=0.12)	33.0 ± 19.0 vs. 83.0 ± 31.1 (p<0.01*)
Surrounding liver tissue (Complete vs. Incomplete)	97.3 ± 30.2 vs. 105.0 ± 37.2 (p=0.70)	120.4 ± 30.1 vs. 101.3 ± 15.8 (p=0.12)	108.3 ± 32.5 vs. 119.3 ± 28.7 (p=0.47)	102.5 ± 14.1 vs. 118.7 ± 25.5 (p=0.34)	106.6 ± 23.5 vs. 105.6 ± 28.1 (p=0.96)	110.0 ± 20.4 vs. 128.8 ± 21.5 (p=0.06)
Ratios of tumor to surrounding liver tissue (Complete vs. Incomplete)	0.97 ± 0.39 vs. 0.99 ± 0.50 (p=1.00)	0.25 ± 0.13 vs. 0.67 ± 0.29 (p<0.01*)	0.22 ± 0.10 vs. 0.73 ± 0.37 (p<0.01*)	0.80 ± 0.23 vs. 0.81 ± 0.25 (p=0.78)	0.33 ± 0.18 vs. 0.61 ± 0.32 (p=0.09)	0.31 ± 0.18 vs. 0.67 ± 0.31 (p<0.01*)