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Therapeutic Evaluation of Radiotherapy with Contrast-Enhanced Ultrasound in Non-Resectable Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombosis

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Background: Therapeutic evaluation of 3-dimensional conformal radiotherapy (3DCRT) is rarely reported for non-resectable hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT). The aim of this study was to determine the value of contrast-enhanced ultrasound (CEUS) in evaluating the therapeutic response of HCC with PVTT treated with 3DCRT.

Material/Methods: PVTT reduction rate in the study was determined after 3DCRT using time intensity curve (TIC) analysis software before and after radiotherapy. Seventy-nine HCC patients with PVTT treated with 3DCRT were studied. HCC and PVTT were performed by CEUS, before and after 3DCRT, over time. The parameters of blood flow, including arrival time (AT), time to peak (TTP), peak intensity (PI), washout time (WT), and area under the curve (AUC), were quantified and evaluated on still images by CEUS.

Results: After 3DCRT, typing and staging of PVTT in 38 patients was decreased, the reduction rate was 48.1%. HCC was effective in 45 patients, the effective rate was 57%; No differences were found between the PVTT reduction rate and the HCC effective rate ($\chi^2=2.96, P>0.05$). In the effective group, the PI and AUC of HCCs and PVTTs after 3DCRT were significantly lower than before 3DCRT, while the other parameters of TIC were not significantly different before and after 3DCRT.

Conclusions: CEUS might be a useful monitoring option for the evaluation of HCC with PVTT treated with 3DCRT. CEUS might be useful as an important choice for monitoring and evaluation HCC with PVTT after 3DCRT. TIC parameters might provide quantitative data for efficacy evaluation, which helps to modify treatment strategies timely and accurately.

MeSH Keywords: **Carcinoma, Hepatocellular • Radiotherapy, Computer-Assisted • Ultrasonography, Doppler**

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Background

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death in the world [1]. In 2012, China alone account for about 50% of the total number of new liver cancer cases and deaths that occurred worldwide [2], with 5-year survival rates only reaching 10.1% [3].

Portal vein tumor thrombosis (PVTT) is a common complication of HCC that often leads to intrahepatic and/or distant metastasis and has a poor outcome [4]. According to the Barcelona Clinic Liver Cancer classification system, HCC patients with PVTT are recognized as Barcelona Clinic Liver Cancer Stage C.

The presence of PVTT can help better stratify HCC patients for therapeutic strategies. Sorafenib used to be recommended for non-resectable patients with PVTT [5–7]. However, median survival of patients with sorafenib only reached 6.5 months [8]. The presence of portal vein hypertension, tumor dissemination, and the deterioration of liver function are common in patients with PVTT [9]. Therapeutic strategies, including surgical resection and transarterial chemoembolization (TACE), are limited [10,11].

For these patients, 3-dimensional conformal radiotherapy (3DCRT) has gradually become the main treatment in clinics, owing to the advancement of radiation technology that can maximize the protection of normal tissue at the same time as providing tumor treatment [12–14]. The 3DCRT efficiency has been recommended by Chinese expert consensus on multidisciplinary treatment of HCC combined with PVTT (2016 Edition) [15], and also recognized by clinical experts for survival rate and quality of life of advanced hepatic carcinoma patients. However, therapeutic monitoring of radiotherapy has been rarely reported.

PVTT is usually diagnosed using imaging. Contrast-enhanced ultrasound (CEUS) is the most convenient method of detecting PVTT [16]. CEUS has an excellent spatial and temporal resolution, and assesses quantitatively microcirculation perfusion of the liver parenchyma and tumors using microbubble ultrasound contrast agent [17]. One of our previous studies showed that CEUS and contrast-enhanced computed tomography (CT) had good consistency in diagnosis and classification of portal vein tumors. CEUS might prove to be a perfect complement to enhanced CT in the patients with small tumor thrombus [18]. In addition, CEUS can be quantitatively analyzed for clinicians. CEUS has already been successfully used in monitoring anti-angiogenic therapies for tumors [19,20] and assessments before and after radiotherapy of HCC [21,22]. However, therapeutic evaluation of 3DCRT has been rarely reported for non-resectable HCC with PVTT.

The present study was designed to quantitatively analyze before and after 3DCRT of non-resectable HCC with PVTT by commercially available software and explore the differences in perfusion parameters.

Material and Methods

Patients

This retrospective study was approved by the institutional review board of Affiliated Tumor Hospital of Guangxi Medical University. This study included 79 advanced HCC patients with PVTT (67 males and 12 females, 33–71 years old, mean age 52.8 years) who underwent CEUS at our hospital from January 1, 2014 to December 31, 2016. All cases met the following criteria: a) histopathologically or radiologically diagnosed as HCC with PVTT; b) non-resectable or medically unsuitable for resection; c) without any cancer-related treatments before our study; d) according to the Child-Pugh liver disease classification, patients were Child-Pugh class A or B; e) without distant metastasis; and f) all patients were positive for serum hepatitis B virus (HBV) surface antigen

Imaging protocol

GE E9 color Doppler ultrasonic diagnostic unit with a probe at frequency of 2–4 MHz based on techniques of coding phase inversion (CPI) and Tru angiography detection (TAD) were applied, contrast agent was 6 sulfur hexafluoride microbubbles (Sonovue, Bracco, Italy).

Radiation treatment

Patients were treated with simple hypo-fractionated 3DCRT, application of 8MVx-ray linear accelerator or Elekta 6MV x-ray linear accelerator (Philips), segmentation dose of irradiation of 3–6 Gy (median 4.45 Gy), irradiation times of 7–21 (median 12), 3–4 times a week, total course of 2–7 weeks (median 4 weeks).

CEUS image evaluation

Patients were assessed for toxicities on a weekly basis during 3DCRT and once every 3 months thereafter. Treatment associated acute and late toxicities were scored according to the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). Tumor response was assessed and divided into effective (complete remission + partial remission) and ineffective (stable disease + progressive disease) groups using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria [23]. CEUS scans were performed on HCC patients with PVTT before and after completion of radiotherapy, over time.

Table 1. PVTT typing before and after 3DCRT.

Before	Case	After				
		Negative	I	II	III	IV
I	11	5	6	0	0	0
II	29	3	9	15	1	1
III	31	0	5	12	13	1
IV	8	0	0	1	3	4

Table 2. Parameters of TIC for HCC in before and after 3DCRT groups.

	Effective group		P	Ineffective group		P
	Before 3DCRT	After 3DCRT		Before 3DCRT	After 3DCRT	
AT	9.91±2.29	9.82±2.17	0.121	10.02±2.57	9.94±2.96	0.194
TTP	31.12±5.32	30.99±5.77	0.347	30.51±4.89	30.14±5.02	0.589
PI	50.51±5.99	11.79±6.12	0.002	49.76±5.99	48.99±5.87	0.237
WT	92.57±6.64	92.41±6.68	0.234	91.38±5.61	91.17±5.21	0.091
AUC	2257±234	512±94	0.001	2225±228	2218±206	0.267

Table 3. Parameters of TIC for PVTT in before and after 3DCRT groups.

	Effective group		P	Ineffective group		P
	Before 3DCRT	After 3DCRT		Before 3DCRT	After 3DCRT	
AT	10.14±4.18	10.22±3.99	0.534	10.09±3.97	9.98±4.11	0.226
TTP	30.98±5.79	30.67±6.03	0.298	31.54±5.16	31.21±6.04	0.361
PI	36.47±5.78	13.15±4.79	0.001	37.94±6.03	36.89±6.21	0.179
WT	98.53±5.35	97.38±5.94	0.192	98.67±5.67	98.91±5.86	0.133
AUC	2237±219	693±106	0.001	2274±212	2255±208	0.462

First, conventional scan was processed on hepatic lobes and segments as well as intrahepatic portal vein system. Then CEUS was continuously observed in real-time for 5 minutes. Last, perfusion parameters, including arrival time (AT), time to peak (TTP), peak intensity (PI), washout time (WT), and area under the curve (AUC), were obtained through time intensity curve (TIC) software.

Statistical analysis

All data presented as mean ± standard deviation (SD) were analyzed by SPSS 16.0 software (SPSS, Chicago, IL, USA). The chi-square test was used to verify the efficacy of 3DCRT on PVTT and HCC. The paired *t*-test was used to verify the perfusion parameters of CEUS before and after radiotherapy. *P*<0.05 was considered as statistically significant.

Results

Short-term efficacy of HCC after 3DCRT

According to the mRECIST criteria [21], there were 45 cases (57.0%) of partial remission (PR), 29 cases (36.7%) of stable disease (SD) and 5 cases (6.3%) of progressive disease (PD).

3DCRT efficacy on PVTT and HCC

After 3DCRT, there were 38 cases that had PVTT type decreasing [24], and the downstaging rate was 48.1% (38 out of 79) (Table 1). There were 45 cases of PR in HCC, the efficiency rate was 57% (45 out of 79). There were no statistical differences between the downstaging rate of PVTT and the efficiency rate of HCC ($\chi^2=2.96$, *P*=0.126). Therefore, the downstaging rate of PVTT and efficiency rate of HCC was consistent.

Quantification analysis of CEUS before and after 3DCRT

The AT, TTP, PI, WT, and AUC values of HCCs and PVTTs are summarized in Tables 2 and 3 respectively. In the effective group, the PI and AUC of HCCs and PVTTs before 3DCRT were significantly stronger than after 3DCRT ($P < 0.05$), while time-dependent parameters of HCCs and PVTTs, including AT, TTP, and WT, were not significantly different between before and after radiotherapy ($P > 0.05$) (Figure 1). In the ineffective group, all of the parameters of HCCs and PVTTs were not significantly different before and after of 3DCRT ($P > 0.05$) (Figures 1–4).

Discussion

Previous studies have reported on the utility of CEUS modality for the assessment of therapeutic interventions such as transcatheter arterial chemoembolization (TACE) [25,26], radiofrequency ablation (RFA) [27], as well as proton-treated [22] in HCC. However, as yet, the findings for 3DCRT-treated HCC with PVTT by CEUS have not been studied. Therefore, we prospectively assessed CEUS for evaluating the therapeutic effect of HCC with PVTT treated with 3DCRT.

In the present study, we investigated the ability of CEUS perfusion parameters to evaluate the monitoring therapies of non-resectable HCC patients with PVTT before and after 3DCRT. The CEUS perfusion parameters of patients were analyzed before and after radiotherapy. There were 79 HCC patients with PVTT treated by 3DCRT after 3 months; over time, the total effective rate of HCC was 57% and the PVTT type downstaging rate was 48.1%. The downstaging rate of PVTT and the efficiency rate of HCC were consistent. In the effective group, the PI and AUC of HCCs and PVTTs before 3DCRT were significantly stronger than after 3DCRT ($P < 0.05$). In the ineffective group, all of the parameters of HCCs and PVTTs were not significantly different before and after of 3DCRT.

3DCRT as a palliative treatment, the blood flow in radiotherapy HCCs does not reduce immediately, but, rather, decreases gradually [28]. This is in contrast to other therapeutic modalities, including chemoembolization and radiofrequency ablation treatments, in which the blood flow disappears immediately after treatment is completed. PVTT may obstruct the portal vein blood flow of the tumor and even the corresponding segment of liver parenchyma, so as to influence perfusion parameters. These pathological differences might lead to the characteristic findings on CEUS.

The mRECIST criteria are used to assess the efficacy of solid tumors based on tumor lesions and are often assessed by CT or MRI. The continuous formation of tumor neovascularization is an important basis for tumor growth. After tumor treatment,

there is usually a change in tumor microcirculation blood perfusion, which in turn affects the number and growth of tumor cells, and then changes of tumor diameter appear [29–31]. In addition, it is difficult to measure characteristics due to the amorphous configuration of PVTT. The mRECIST is generally not recommended for treatment evaluation of PVTT [32]. As a functional imaging method, CEUS may accurately reflect the functional and metabolic information of the microcirculatory structure in the perfusion area. CEUS detection of the tumor vascularity in sensitive modality is superior to mRECIST based on CT or MRI, which are difficult to use to evaluate the therapeutic efficacy immediately after the treatment.

Our study results demonstrated that the PI of HCCs and PVTTs after 3DCRT were significantly lower than before 3DCRT in the effective group. Meanwhile, the PI of HCCs and PVTTs were not significantly different before and after 3DCRT. The gradual damage and decrease of tumor microcirculation is a characteristic feature of 3DCRT. The properties and parameters of TIC are related to tissue structure and characteristics of microcirculation [33]. PI reflecting the balance between inflow and outflow of microbubbles, which is related to the number of microbubbles aggregation, can reflect the blood perfusion state in the region through quantization the PI of the contrast agent. Our results confirmed that the amount of contrast agent that entered microcirculation of HCC with PVTT was reduced each time after 3DCRT, and that the microcirculation structure of HCC with PVTT was destroyed; these findings were similar in the present study to that of these changes observed through CT images [22]. However, the use of contrast agent for CT is limited in patients with chronic renal failure, and CT scan involves radiation exposure.

Our study results showed that the AUC of HCCs and PVTTs after 3DCRT were significantly lower than before 3DCRT in the effective group. Radiotherapy of tumor tissues suffers when microcirculation structure is destroyed. It can affect blood flow in and out of tumor microcirculation, and the contrast microbubble is similar changed. The AUC is associated with blood flow in and out of the tumor, so the AUC of the effective group was changed after radiotherapy. However, the AUC was affected by all of the TIC parameters, so, it was not clear what caused the reported study results.

This study was limited by a small sample size; a future study with a larger patient population is essential to validate the result. In addition, this study was based on a single-center study, and thus selection bias might exist. In addition, this study was not a comparison with other imaging methods; a future study with a larger sample size is essential to compare the 2 types of contrast media.

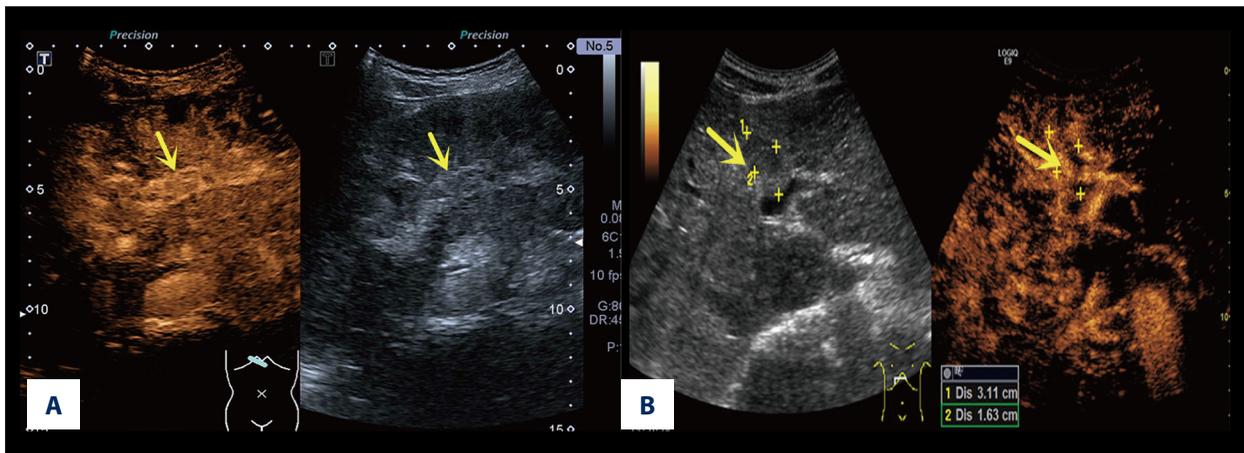


Figure 1. Conventional ultrasound and CEUS imaging before and after PVTT irradiation. Both PVTT size and enhanced intensity decreased from type II (A) to type I (B) after irradiation. CEUS – contrast-enhanced ultrasound; PVTT – portal vein tumor thrombus.

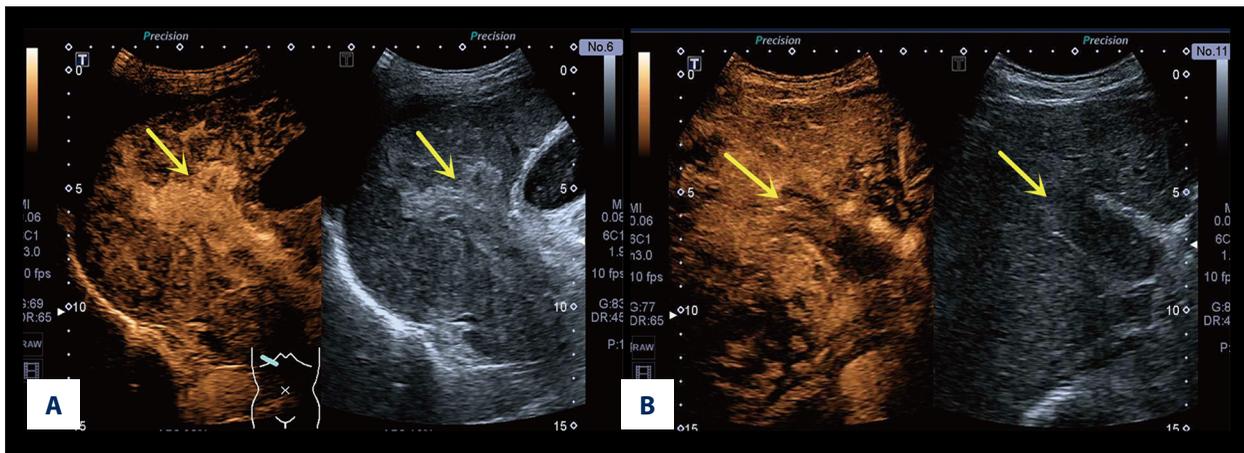


Figure 2. Conventional ultrasound and CEUS imaging before (A) and after (B) PVTT irradiation. PVTT size in type III had no change before and after irradiation but enhanced intensity decreased. CEUS – contrast-enhanced ultrasound; PVTT – portal vein tumor thrombus.

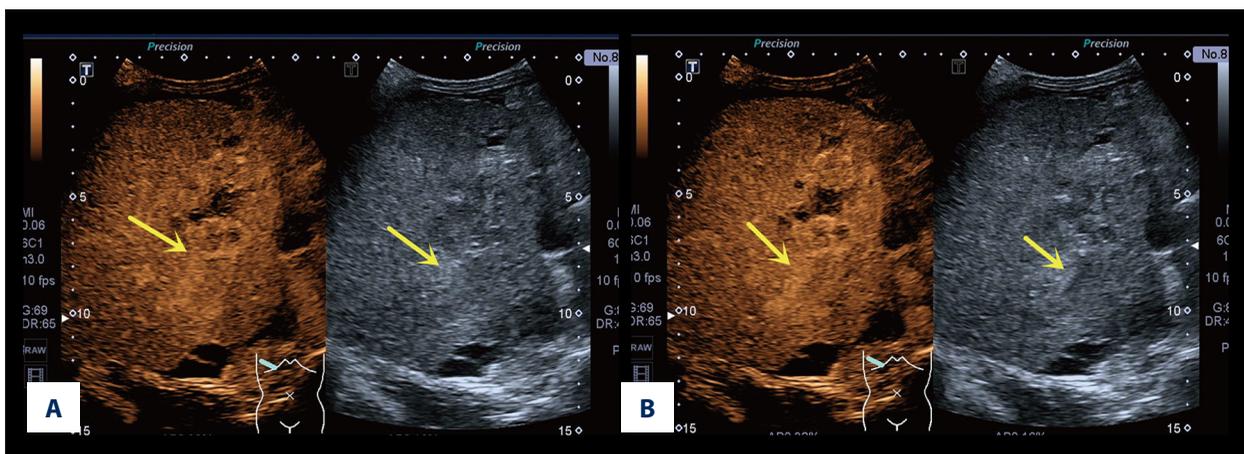


Figure 3. Conventional ultrasound and CEUS imaging before and after PVTT irradiation. Both PVTT size and enhanced intensity had no change before (A) and after (B) irradiation in 1 case with low effective radiotherapy effect. CEUS – contrast-enhanced ultrasound; PVTT – portal vein tumor thrombus.

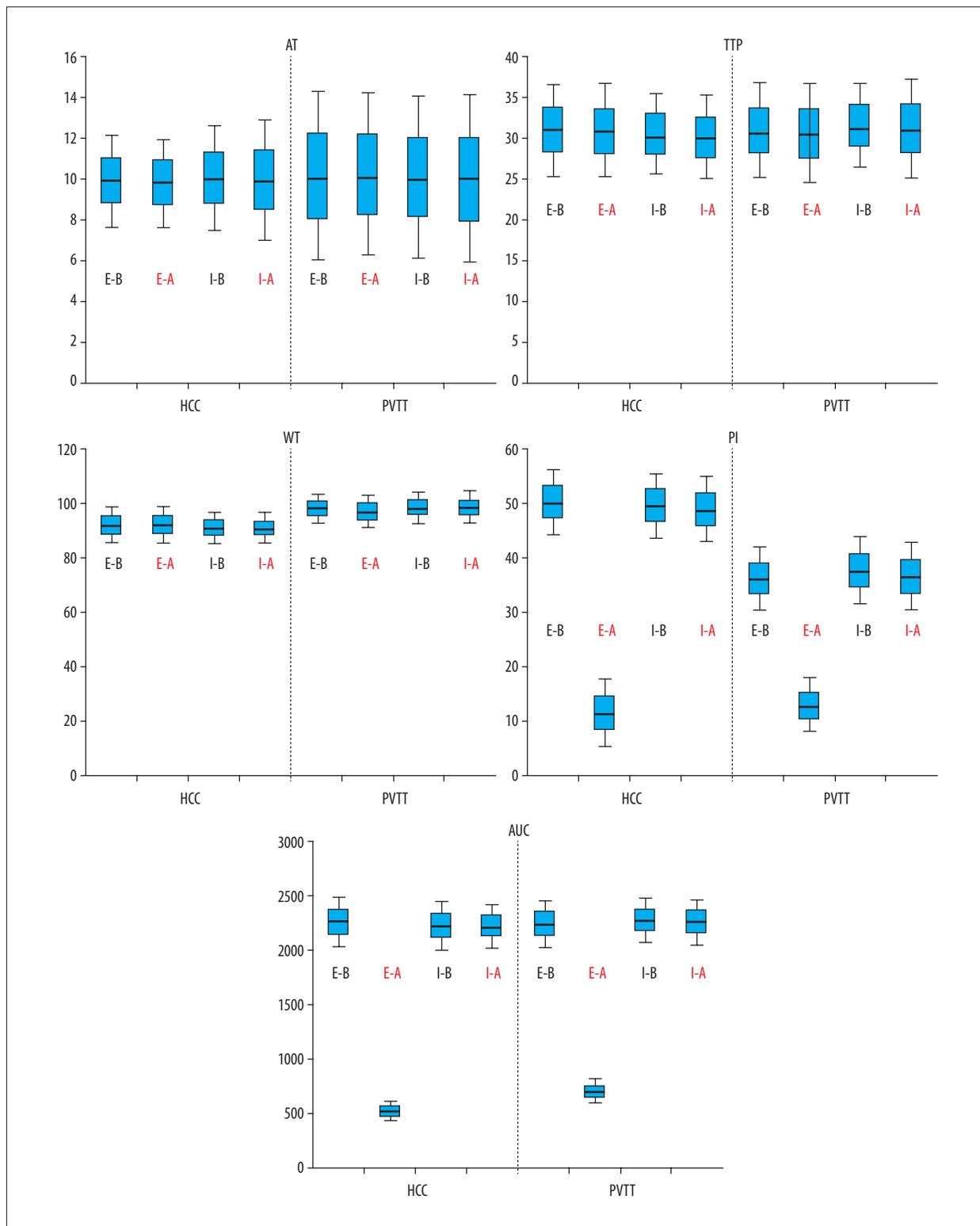


Figure 4. Comparison of CEUS parameters of before and after 3DCRT groups in HCC and PVTT for all lesions: (E-B) before 3DCRT in the effective group; (E-A) after 3DCRT in the effective group; (I-B), before 3DCRT in the ineffective group; (I-A), after 3DCRT in the ineffective group. CEUS – contrast-enhanced ultrasound; 3DCRT – 3-dimensional conformal radiotherapy; HCC – hepatocellular carcinoma; PVTT – portal vein tumor thrombosis; AT – arrival time; TTP – time to peak; PI – peak intensity; WT – washout time; AUC – area under the curve.

Conclusions

3DCRT might provide an effective treatment for advanced liver cancer. The PVTT reduction rate and HCC efficiency had good consistency. CEUS might evaluate the therapeutic effect by changes in tumor microcirculation information after 3DCRT. CEUS is reported to be superior to mRECIST on CT or MRI for assessing HCC and PVTT microcirculation perfusion changes after 3DCRT. CEUS might be considered an important choice

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for monitoring and evaluation therapeutic efficacy after 3DCRT. PI and AUC in the TIC parameters might provide quantitative data for the evaluation of efficacy after 3DCRT, which then helps to modify the treatment strategy timely and accurately.

Conflict of interests

None.