Program Digest, 2019 IEEE International Ultrasonics Symposium (IUS)
Glasgow, Scotland, October 6-9, 2019

Predicting Long Term HCC Response to Radioembolization Using Contrast-Enhanced Ultrasound 1-2 Weeks Post Treatment

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***Abstract*—This study evaluated whether quantitative contrast-enhanced ultrasound (CEUS) can predict long term response of hepatocellular carcinoma (HCC) to Yttrium-90 (Y-90) radioembolization therapy. Twelve patients scheduled for Y-90 radioembolization therapy of a previously untreated HCC underwent CEUS at 3 time points: immediately following treatment, and 7 and 14 days post-treatment. Ultrasound imaging was performed using a Siemens S3000 Helx scanner with a C6-1 probe in dual 2D B-mode/contrast mode. Treatment response was evaluated with MRI 3-4 months post-treatment using modified response evaluation criteria in solid tumors (mRECIST) by two experienced radiologists in consensus. CEUS data was analyzed by quantifying tumor perfusion and residual fractional vascularity, using contrast time intensity curves that were created off-line. At 7 days post-treatment, the patient with stable disease exhibited significantly greater tumor vascularity (70.96 ± 7.63%) than patients with partial response (30.88 ± 20.56%, $p < 0.0001$) and complete response (13.64 ± 10.97%, $p < 0.0001$). Additionally, patients with stable disease exhibited significantly greater tumor perfusion 14 days post-treatment (2.33 ± 0.22 ml/s*mg) than both partial response (0.05 ± 0.05 ml/s*mg, $p < 0.0001$) and complete response patients (0.47 ± 0.46 ml/s*mg, $p < 0.0001$). Although larger sample sizes and longer follow up are needed to fully evaluate the clinical impact of CEUS, it appears to provide an earlier indicator of Y-90 treatment response than MRI.**

Keywords—contrast enhanced ultrasound, HCC, perfusion

I. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide and the fastest growing malignancy in the United States [1,2]. HCC represents approximately 90% of primary liver cancers in the United States [1], and the 5-year survival remains poor at approximately 10-12% [1,2]. Only about 30% of patients presenting with HCC are eligible for resection, and liver transplant requires relative contained disease state (1 lesion less than 5 cm or up to 3 lesions less than 3 cm) [3,4]. For patients with unresectable HCC, there is no standard treatment [3], but transarterial embolization is one of the recommended treatments. Embolization can be performed using transarterial chemoembolization (TACE) or Yttrium-90 (Y-90) radioembolization. Radioembolization therapy is also recommended for patients with 4 or more lesions, or 2-3 larger (> 3 cm) lesions [5].

Although a relatively new therapeutic option, Y-90 radioembolization is gaining clinical acceptance with several recent studies demonstrating prolonged time to progression [6], increased rate of tumor downstaging and tumor necrosis [7-9], and improved overall quality of life [10] in patients treated with radioembolization relative to traditional chemoembolization. At our institution, radioembolization is performed using TheraSpheres (BTG International, London, United Kingdom), which consist of 20-30 μm glass beads containing Y-90). The TheraSpheres are locally delivered via a catheter temporarily placed in the hepatic artery branches supplying the tumor, thereby providing a localized and sustained release of radiation within the tumor. Y-90 undergoes pure beta emissions as it decays to stable Zirconium-90 with a half-life of 64 hours, average energy emission of 0.94 MeV, and a maximum tissue penetration of 10 mm within the liver [11-13]. Dosages range from 110-150 Gy, but radiation delivered to tumor cells is dependent on distance from the yttrium source. Consequently, tumor response rate after radioembolization is between 25-60% when based on modified response criteria in solid tumors (mRECIST) [13]. Other studies determining treatment outcome based on tumor reduction and vascularity have found response rates of 47-89%, with progression free survival of 13.3 months [6, 14]. Compared to TACE, Y-90 radioembolization seems to have a more rapid effect on tumor reduction, with a lower median time to partial response using RECIST criteria (4.2 months vs. 10.9 months) [13]. Y-90 treatment response is typically monitored with contrast-enhanced MRI or CT performed 1 and 3-4 months after treatment. Earlier determination of treatment response would enable faster retreatments and could potentially improve patient outcomes.

Therefore, this study evaluated the ability of quantitative contrast-enhanced ultrasound (CEUS) performed 1 and 2 weeks post-treatment to predict long term response of HCC to Y-90 radioembolization. Changes in tumor perfusion have been identified as early indicators of HCC treatment response [15-17], and we have previously shown that CEUS can be used to

Funding Sources: National Institutes of Health and Siemens Healthineers

successfully characterize perfusion in liver lesions [18]. CEUS imaging makes use of ultrasound contrast agents (UCA), which are gas filled microbubbles, encapsulated by a lipid or protein shell for stability. These agents are small enough (1-8 μm in diameter), to pass through the pulmonary capillaries, but are still restricted to the vascular system [19]. UCA perfuse into the vasculature of HCC tumors, and their wash-in/wash-out kinetics can be used to characterize liver masses [18]. Our group has demonstrated the exceptional safety and accuracy of CEUS for monitoring HCC response to TACE [18], and have also observed that UCA perfuse into HCC post radioembolization, due to the fact that the large Y-90 beads (20-30μm in diameter) do not completely restrict blood flow to the tumor, especially secondary feeding vessels. Commercially available flash-replenishment packages can be used to visualize and quantify contrast perfusion [20,21]. These flash-replenishment sequences generate relatively high intensity pulses within a selected sector of interest to induce UCA cavitation and destruction, followed by lower intensity imaging to visualize contrast reperfusion [19]. We hypothesize that UCA reperfusion following flash-replenishment ultrasound pulses will reflect changes in tumor perfusion and fractional vascularity, and provide an earlier predictor of Y-90 radioembolization treatment response than standard of care CT or MR imaging.

II. Materials and Methods

As part of an ongoing IRB-approved trial (NCT# 03199274), 12 prospective patients scheduled for radioembolization therapy of a previously untreated HCC provided informed consent to participate in this study. Radiotherapy was performed using segmental delivery of Y90 Therapheres at doses ranging from 117-152 Gy. CEUS exams were performed at three time points (immediate following radioembolization, and 7 and 14 days post-treatment. All imaging was performed using a Siemens S3000 Helx scanner (Siemens Healthineers, Mountain View, CA, USA) with a C 6-1 transducer in dual 2D B-mode/contrast mode during a 10 minutes (0.5 mL/min) infusion of ultrasound contrast agent Optison (GE Healthcare, Princeton, NJ). During each CEUS exam, flash-replenishment sequences were performed at the tumor midline for UCA destruction/replenishment imaging.

Ultrasound contrast time-intensity curves were generated offline using Matlab software (MathWorks, Natick, MA, USA) to quantitatively evaluate residual fractional vascularity and perfusion post-treatment using a segmentation algorithm. Contrast replenishment time intensity curves were fit to a 2-parameter exponential recovery curve: $VI = \alpha(1 - e^{\beta t})$, where VI represents video intensity; α (in dB) represents the asymptotic plateau correlative of the microvessel cross-sectional area; and β (in mm/s) represents the blood velocity. As a reference standard, treatment response was evaluated with MRI using modified response evaluation criteria in solid tumors (mRECIST) 3-4 months post-treatment by two radiologists in consensus.

Statistical analysis was performed with GraphPad Prism 7 (GraphPad Software, La Jolla, CA), with p-values below 0.05 indicating statistical significance. Comparisons between treatment groups were performed using a one-way ANOVA with Bonferroni correction for multiple comparisons. Error bars represent standard deviation.

III. Results and Discussion

To date, treatment responses have included 1 case of stable disease (SD), 8 cases of partial response (PR), and 3 cases of complete response (CR) based on the mRECIST scoring. Within 7 days post treatment, the tumor showing SD 4 months post treatment had significantly greater residual tumor vascularity on CEUS (70.96 ± 7.63% across multiple slices) than the tumors in PR (30.88 ± 20.56%) and CR groups (13.64 ± 10.97%) ($p < 0.0001$). Importantly, tumors in the PR group also showed significantly more residual tumor vascularity than tumors in the CR group at this time point ($p = 0.0034$).

Representative images of residual tumor vascularity for each response group at 7 days post-treatment are shown in Figure 2. Additionally, representative images of a patient with complete response (CR) showing progressive loss of tumor fractional vascularity at each study time point (immediately following treatment, 7 days post-treatment, and 14 days post-treatment) are shown in Figure 3.

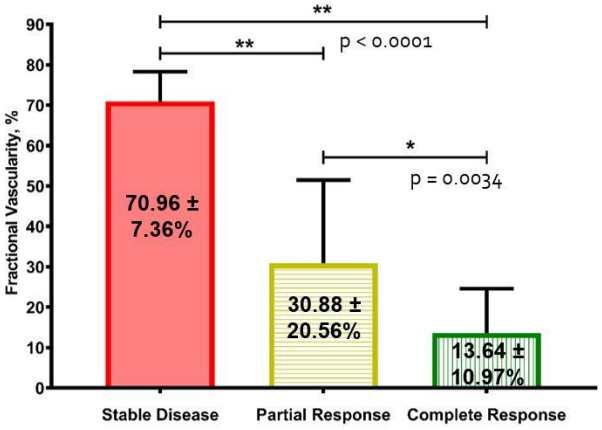

Fig. 1. Summary of tumor vascularity at 7 days post-treatment in different clinical outcome groups, n=12.

Interestingly, when analyzing tumor perfusion (Figure 4), tumors in the CR group showed greater tumor perfusion than tumors in the PR group at both 7 days (0.35 ± 0.39 vs. 0.11 ± 0.16 ml/s*mg; $p = 0.0004$) and 14 days post-treatment (0.47 ± 0.46 ml/s*mg vs. 0.05 ± 0.05 ml/s*mg, $p < 0.0001$), likely due to post-treatment inflammatory response. However, tumors with SD exhibited significantly increased tumor perfusion at 14 days post-treatment (2.33 ± 0.22 ml/s*mg) than tumors in both PR and CR groups ($p < 0.0001$). Additionally, SD tumor perfusion was significantly increased at 14 days compared to 7 days (0.15 ± 0.07 ml/s*mg; $p < 0.0001$), suggesting a failure to respond to treatment within the first 2 weeks. While these findings are based on a limited sample size, these results

suggest that quantitative CEUS performed shortly after treatment can be used to predict longer-term response of HCC tumors to Y-90 radioembolization therapy.

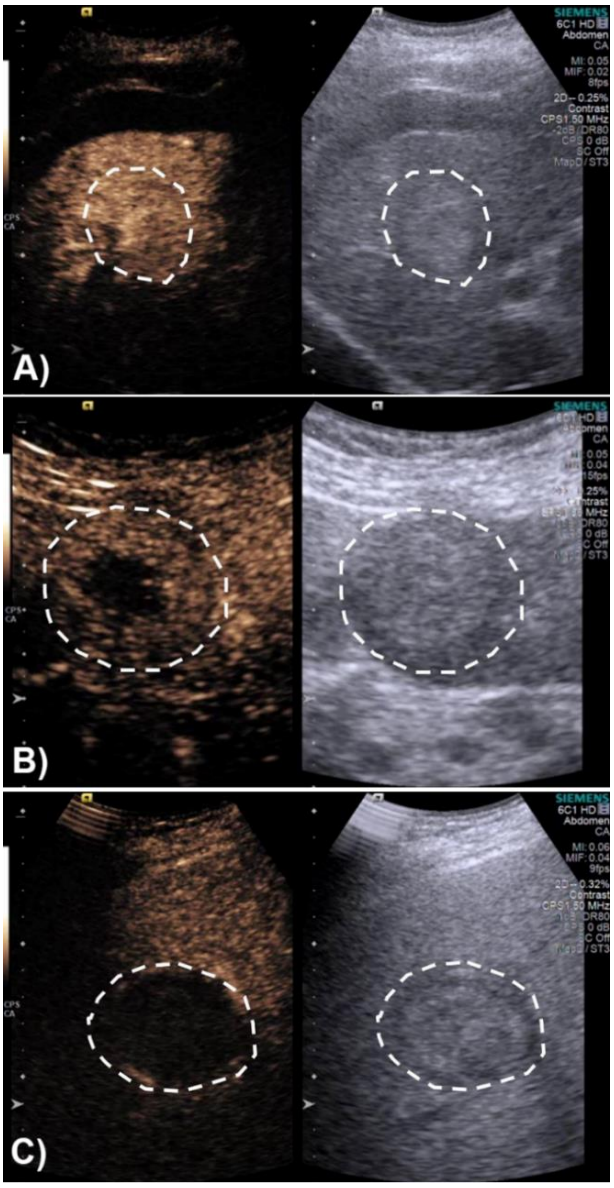

Fig. 2. Representative CEUS images of HCC tumors 7 days post-radioembolization, tumors are deliniated by white circles. Left image is CEUS, right is grayscale ultrasound. A) Tumor classified as stable disease (SD) with the entire tumor region showing echogenicity. B) Tumor classified as partial response (PR), with a hypoechoic region within the tumor suggesting necrotic tissue. C) Tumor classified as complete response (CR), with most of the tumor area appearing hypoechoic suggesting mostly necrotic tissue.

IV. Conclusion

While larger sample sizes and longer follow up is required to fully evaluate effectiveness, CEUS appears to provide an earlier indicator of Y-90 radioembolization response at 2 weeks compared to the current clinical standard of care MRI performed 3-4 months post-treatment.

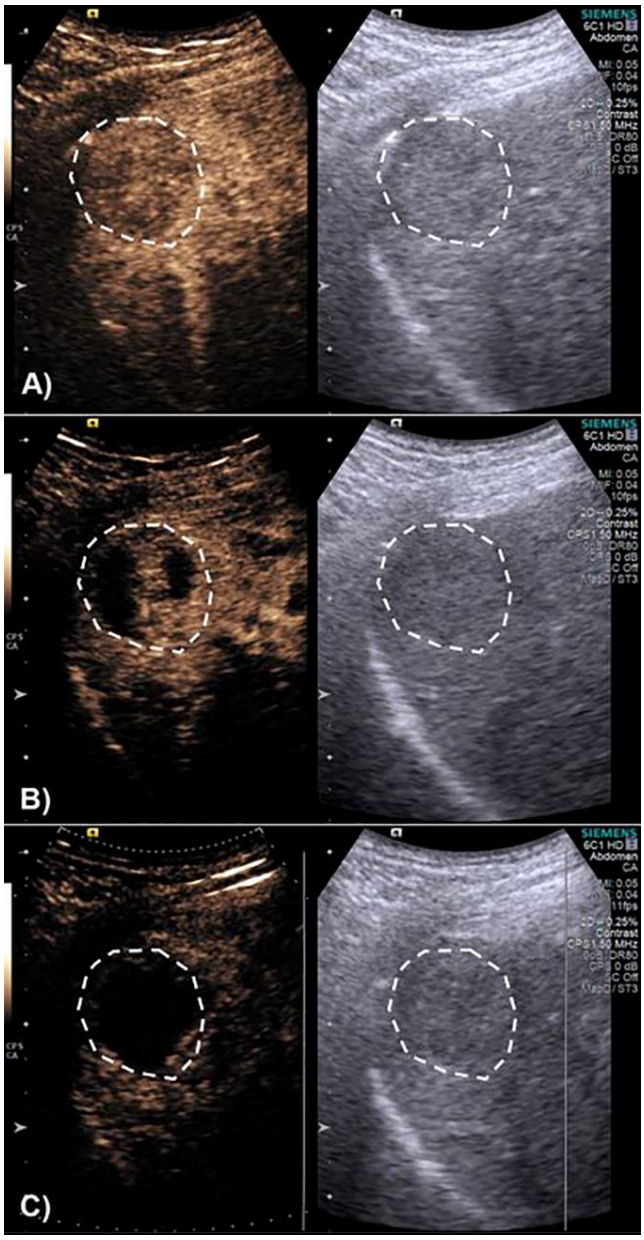

Fig. 3. Representative CEUS images of a CR patient from all 3 study time points, left image is CEUS, right image is grayscale ultrasound. A) CEUS imaging immediately following radioembolization, with the entire tumor region showing echogenicity. B) CEUS imaging at 7 days post-treatment, with small hypoechoic regions within the tumor suggesting necrotic tissue. C) CEUS imaging at 14 days post-treatment, with most of the tumor area appearing hypoechoic suggesting mostly necrotic tissue.

Acknowledgments

The authors would like to thank Jesse Civan MD, Scott Keith PhD, and Kristen Bradigan RN from Thomas Jefferson University for their contributions to this project. Additionally, we thank Siemens Healthineers for equipment support. This work was supported by NIH grants R01 CA194307, R21 CA190926, and F32 AR072491.

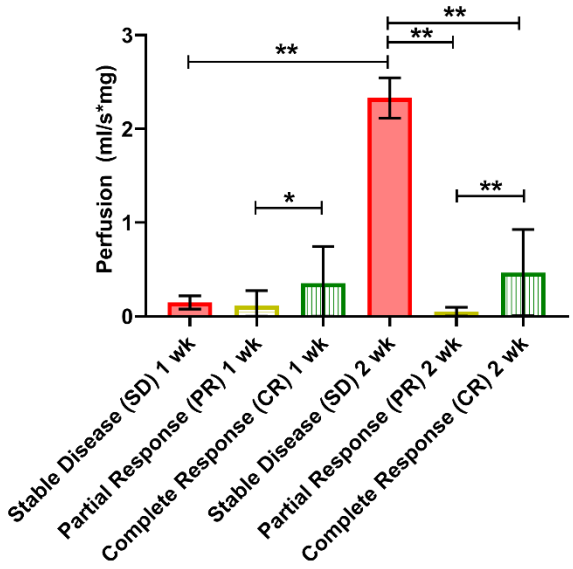

Fig. 4. Summary of tumor perfusion at 7 and 14 days post-treatment separated by treatment group, n=12.

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