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Volumetric assessment of tumour response using functional MR imaging in patients with hepatocellular carcinoma treated with a combination of doxorubicin-eluting beads and sorafenib

Celia Pamela Corona-Villalobos,

The Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, School of Medicine, 600 N. Wolfe St., MRI 110B, Baltimore, MD 21287, USA

Vivek Gowdra Halappa,

The Russell H. Morgan Department of Radiology and Radiological Sciences, School of Medicine, Johns Hopkins University, 600 N. Wolfe St., MRI 143, Baltimore, MD 21287, USA

Jean-Francois H. Geschwind,

Department of Vascular and Interventional Radiology, School of Medicine, Johns Hopkins University, 1800 Orleans Street, Sheik Zayed Tower, Suite 7203, Baltimore, MD 21287, USA

Susanne Bonekamp,

The Russell H. Morgan Department of Radiology and Radiological Sciences, School of Medicine, Johns Hopkins University, 600 N. Wolfe St., MRI 143, Baltimore, MD 21287, USA

Diane Reyes,

Department of Vascular and Interventional Radiology, School of Medicine, Johns Hopkins University, 1800 Orleans Street, Sheik Zayed Tower, Suite 7203, Baltimore, MD 21287, USA

David Cosgrove,

Department of Oncology, Johns Hopkins University, School of Medicine, 401 N Broadway, CRB I, Suite 487, Baltimore, MD 21287, USA

Timothy M Pawlik, and

Department of Surgical Oncology, Johns Hopkins University, School of Medicine, 600 N. Wolfe Street, Blalock 688, Baltimore, MD 21287, USA

Ihab R Kamel

The Russell H. Morgan Department of Radiology and Radiological Sciences, School of Medicine, Johns Hopkins University, 600 N. Wolfe St., MRI 143, Baltimore, MD 21287, USA

Celia Pamela Corona-Villalobos: ccorona1@jhmi.edu; Vivek Gowdra Halappa: vivekhalappa86@gmail.com; Jean-Francois H. Geschwind: jgeschw1@jhmi.edu; Susanne Bonekamp: susanne.bonekamp@gmail.com; Diane Reyes: dreyes@jhmi.edu; David Cosgrove: dcosgro2@jhmi.edu; Timothy M Pawlik: tpawlik1@jhmi.edu; Ihab R Kamel: ikamel@jhmi.edu

Abstract

Objective—To prospectively assess treatment response using volumetric functional magnetic resonance imaging (MRI) metrics in patients with hepatocellular carcinoma (HCC) treated with the combination of doxorubicin-eluting bead–transarterial chemoembolization (DEB TACE) and sorafenib.

Methods—A single center study enrolled 41 patients treated with systemic sorafenib, 400 mg twice a day, combined with DEB TACE. All patients had a pre-treatment and 3–4 week post-treatment MRI. Anatomic response criteria (RECIST, mRECIST and EASL) and volumetric functional response (ADC, enhancement) were assessed. Statistical analyses included paired Student's *t*-test, Kaplan-Meier curves, Cohen's Kappa, and multivariate cox proportional hazard model.

Results—Median tumour size by RECIST remained unchanged post-treatment (8.3 ± 4.1 cm vs. 8.1 ± 4.3 cm, $p=0.44$). There was no significant survival difference for early response by RECIST ($p=0.93$). EASL and mRECIST could not be analyzed in 12 patients. Volumetric ADC increased significantly (1.32×10^{-3} mm²/sec to 1.60×10^{-3} mm²/sec, $p<0.001$), and volumetric enhancement decreased significantly in HAP (38.2 % to 17.6 %, $p<0.001$) and PVP (76.6 % to 41.2 %, $p<0.005$). Patients who demonstrated 65 % decrease PVP enhancement had significantly improved overall survival compared to non-responders ($p<0.005$).

Conclusion—Volumetric PVP enhancement was demonstrated to be significantly correlated with survival in the combination of DEB TACE and sorafenib for patients with HCC, enabling precise stratification of responders and non-responders.

Keywords

Volumetric functional MRI; DEB-TACE; Sorafenib; Diffusion-weighted MRI; Treatment response

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It claims more than 500,000 lives annually and is the third leading cause of cancer deaths worldwide [1, 2]. Even though the best modality of treatment in patients with HCC is resection/transplantation, most of the patients present with advanced disease (including involvement of lymph nodes, spread to distant sites, and inadequate future liver remnant) or compromised performance status at the time of diagnosis, and are deemed to be unresectable [3]. Intra-arterial therapies (IAT), including conventional transarterial chemoembolization (TACE), radioembolization and the recent molecular targeted treatment with sorafenib, have opened new treatment strategies against HCC [4]. TACE has been considered the standard of care for patients with intermediate stage Barcelona Clinic Liver Cancer (BCLC) stage, with an expected survival of around 20 months for those patients [5, 6].

The advent of new drug delivery systems such as doxorubicin-eluting bead–transarterial chemoembolization (DEB TACE) has further helped patients with HCC by significantly lowering liver toxicity and systemic drug exposure, while at the same time increasing drug delivery to the tumour compared to conventional transarterial chemoembolization (cTACE) [7–9]. DEB TACE was shown to be safe and effective in achieving local tumour control in

patients with unresectable HCC [7]. Molecularly targeted therapy with sorafenib significantly improved survival of patients with advanced HCC (compared to placebo), resulting in US Food and Drug Administration (FDA) approval. Sorafenib acts by inhibiting serine threonine kinases and the receptor tyrosine kinase of vascular endothelial growth factor (VEGF), as well as platelet-derived growth factor (PDGF) receptors [4, 8].

A major limitation of cTACE is the high recurrence rate after treatment. This is often attributed to the profound ischemia caused by TACE, and the resultant significant upregulation of angiogenesis and increase in VEGF expression that peaks between 24 and 36 hours after treatment [9, 10]. Therefore, the scientific rationale for combining sorafenib with DEB TACE is to counteract the increased expression of VEGF post-TACE, and thus improve its efficacy. The combination of DEB TACE and sorafenib was already shown to be well tolerated and safe in patients with unresectable HCC [11, 12]. Assessment of treatment response after each TACE cycle is important, since it helps determine the need for re-treatment. Although this concept of imaging response appears trivial, it is actually extremely complex, because conventional anatomical metrics of change in tumour size as assessed by Response Evaluation Criteria in Solid Tumours (RECIST) are inadequate to precisely determine the extent of tumour necrosis after TACE [13, 14]. In order to address these limitations, new criteria were established that equated lack of contrast enhancement in the tumour with necrosis (European Association for study of Liver Disease [EASL] and modified RECIST [mRECIST]) [15]. Studies have also demonstrated the value of volumetric apparent diffusion coefficient (ADC) and volumetric enhancement for assessment of early treatment response in patients with primary and metastatic liver malignancies treated with TACE [16–19]. Volumetric assessment of tumour response provides better understanding of tumour microvasculature and treatment induced necrosis with quantitative measurements of the entire tumour volume as compared to axial plane measurements [20].

To date, response assessment by volumetric functional magnetic resonance imaging (MRI) has not been reported in patients with HCC treated by combination DEB TACE and sorafenib. Hence, the objective of this study was to prospectively assess treatment response using volumetric functional MRI metrics, including apparent diffusion coefficient (ADC) from diffusion weighted imaging (DWI) and contrast enhanced MRI (CE-MRI), in patients with hepatocellular carcinoma (HCC) treated with the combination of DEB TACE and sorafenib.

Materials and methods

Patient population

The study was approved by the FDA under both a physician-sponsored investigational device exemption (IDE) and investigational new drug (IND), and by our institutional review board. Patients provided written informed consent. Inclusion and exclusion criteria for enrolment into the clinical trial and for image analysis by MRI are described in Fig. 1.

Treatment protocol

The procedure for DEB TACE was performed according to our standard Institutional protocol as previously described in the literature [7, 12, 21]. All IATs were performed by a single interventional radiologist (JFG) with 15 years of experience. All procedures were performed without any complications. The treatment protocol for combination DEB TACE and systemic sorafenib that was followed for this clinical trial is described in the literature [11]. Patients were treated by 400 mg twice daily of sorafenib continuously initiated 1 week before DEB TACE. Super selective DEB TACE was administered with a maximum of 100 mg of doxorubicin loaded onto 100 to 300 [μ m] m LC beads [11].

MR imaging technique

Patients underwent our standard institutional liver cancer MRI imaging protocol with pretreatment and 3–4 week post-treatment MRI. MR imaging was performed using a 1.5 T MRI (Siemens MAGNETOM Avanto) using a phased array torso coil. The protocol consisted of T2-weighted (T2W) turbospin-echo images (matrix size, 256×256; slice thickness, 8 mm; interslice gap, 2 mm; TR/TE, 4500/92; received bandwidth, 32 kHz) and breath-hold diffusion weighted echoplanar images (matrix, 128×128; slice thickness, 8 mm; interslice gap, 2 mm; b value=0 s/mm², 750 s/mm²; repetition time, 3,000 ms; echo time, 69 ms; received bandwidth, 64 kHz). Breath-hold unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadopentetate; Magnevist; Bayer, Wayne, NJ) T1-weighted (T1W) three-dimensional fat suppressed spoiled gradient-echo images (field of view, 320–400 mm; matrix, 192×160; slice thickness, 2.5 mm; repetition time, 5.77 ms; echo time, 2.77 ms; received bandwidth, 64 kHz; flip angle, 10°) in the arterial (20 s), portal venous (70 s), and delayed phase (3 min) were also obtained.

MR imaging analysis

Image analysis on the first ten patients was performed by an MR radiologist: Reader 1 and a body fellow (VGH); and Reader 2 (IRK), with 15 and three years of experience in abdominal MRI, respectively. The remaining patients were analyzed by Reader 2 under direct supervision of the more experienced Reader 1. Both anatomic and functional metrics were collected pre-IAT and post-IAT.

Using anatomical metrics, response status of the index lesion was assessed by a single measure according to RECIST (change in tumour size) [22], and mRECIST (change in the enhancing part of the tumour in the axial plane) [15], and a bi-dimensional measure according to EASL criteria (change in the enhancing area of the tumour) [23]. According to RECIST, mRECIST and EASL patients were classified as Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD), as described in Table 1.

Using volumetric functional metrics, response status of the index lesion was analyzed using proprietary research software, MR Oncotreat (Siemens Medical Solutions). Our volumetric analysis is under 15 minutes for both pre-IAT and post-IAT. In the first step, patient DICOM data (T2W images, DWI, ADC maps, T1W images pre-contrast, arterial and venous phase images) were imported into MR Oncotreat. In the second step, blue seeds were placed within the tumour and red seeds were placed surrounding the tumour. Tumour

borders were defined with an interactive segmentation technique [24]. The index lesion was segmented to calculate the tumour volume and then ADC values and contrast-enhancement of the entire tumour volume in multiple vascular phases. The software calculated mean volumetric ADC of the entire volume of the tumour and calculated enhancement in the arterial and portal venous phases. Hepatic arterial phase (HAP) enhancement was calculated

from the formula: $HAP = \frac{\text{Arterial Phase Image} - \text{Unenhanced Image}}{\text{Arterial Phase Image}} \times 100$. Portal venous phase (PVP) enhancement was calculated from the formula:

$PVP = \frac{\text{Venous Phase Image} - \text{Unenhanced Image}}{\text{Venous Phase Image}} \times 100$. We used a threshold of 65 % for volumetric enhancement in PVP, based on a previous study that identified and validated the cutoff point to categorize in responders as depicted in Fig. 2, vs. non-responders (Fig. 3) to predict overall survival [19].

The percent change in volumetric tumour ADC (vADC) at follow-up compared to baseline values was calculated using the formula:

$vADC = \frac{\text{Posttreatment Volumetric ADC} - \text{Pretreatment Volumetric ADC}}{\text{Pretreatment Volumetric ADC}} \times 100$. The software automatically provides pretreatment and post-treatment volumetric ADC, enhancement in HAP and PVP, and maps with histograms of ADC and CE-MR in the arterial and portal venous phases. The percent change in volumetric tumour enhancement (vTE) at follow-up compared to baseline values was calculated using

$vTE = \frac{\text{Posttreatment Enhancement} - \text{Pretreatment Enhancement}}{\text{Pretreatment Enhancement}} \times 100$.

Statistical analysis

Results of anatomic and functional data collected from the first ten patients by the two readers were comparable by paired Student's *t*-test. Subsequently, data collected by Reader 2 for the entire cohort were compared using a two-sided paired Student's *t*-test to determine changes in tumour size, tumour volume, volumetric ADC, enhancement in HAP and PVP post-treatment, and to determine differences between responders and non-responders. Inter-reader agreement was determined by Cohen's Kappa (*K*) statistic; < 0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and >0.8–1.0 were considered to represent poor, fair moderate, good and very good agreement, respectively. Survival rates were calculated from the time of first treatment through 15 March 2013, and patients who were still alive were censored for analysis. Kaplan-Meier analysis (K-M) was performed to determine survival differences. The primary endpoint for our study was overall survival from the date of first treatment. Statistical significance was analyzed by log-rank test. Cutoff values for assessing response by volumetric functional MRI were determined by highest log likelihood ratio on univariate regression analysis [25]. Multivariate cox regression analysis was also performed in order to analyze for variables affecting patient survival. Statistical analysis was performed with the SPSS (Version 16.0, SPSS, Chicago, Ill) statistical software package. A *p* value of <0.05 was considered statistically significant.

Results

Demographic data

This prospective study, designed to assess treatment response using multiparametric MR imaging, included data of 41 patients diagnosed with HCC: patients diagnosed by surgery/histology ($n=25$), patients diagnosed by alpha fetoprotein (AFP) ($n=9$), and patients diagnosed by imaging and clinical history ($n=16$). Patients (age 18 years or older) with a diagnosis of unresectable HCC were evaluated as determined by tissue diagnosis from biopsy, by cross-sectional imaging criteria such as the presence of a hypervascular lesion in the arterial phase, displaying wash-out of contrast material during the portal-venous phase in the setting of cirrhosis, or by biological data such as α -fetoprotein level of 200 ng/mL or greater. The mean age of the patient cohort was 62.8 years; and the age range was 31–88 years [Child A ($n=39$), B ($n=2$), Barcelona Clinic Liver Cancer (BCLC) stage A ($n=3$), B ($n=13$), C ($n=25$), Eastern Cooperative Oncology Group (ECOG) 0 ($n=23$), 1 ($n=18$). Patients reported the anticipated dermatologic side effects of systemic Sorafenib administration in the form of rash (53 %) and hand-foot skin reaction (46 %). No other side effects were reported.

Inter-reader agreement

For the first ten patients, results for inter-reader agreement were reported. Pretreatment mean tumour maximum diameter (9.7 cm vs. 9.5 cm), volume (301.9 cm^3 vs. 301.5 cm^3), HAP (37.3 % vs. 36.4 %), PVP (78.7 % vs. 78.1 %) and ADC ($1.30 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.29 \times 10^{-3} \text{ mm}^2/\text{s}$) were not statistically significant ($p>0.05$) for Reader 1 vs. Reader 2, respectively. Similarly, post-treatment mean tumour maximum diameter (9.4 cm vs. 9.3 cm), volume (245.1 cm^3 vs. 243.4 cm^3), arterial enhancement (19.2 % vs. 18.4 %), venous enhancement (47.4 % vs. 46.9 %) and ADC ($1.52 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.51 \times 10^{-3} \text{ mm}^2/\text{s}$) were not statistically significant ($p>0.05$) for Reader 1 vs. Reader 2, respectively. There was very good agreement between Reader 1 and Reader 2 for pretreatment measures for mean tumour maximum diameter ($K=0.82$, CI 0.77–0.88), tumour volume ($K=0.85$, CI 0.81–0.90), HAP ($K=0.86$, CI 0.81–0.92) and PVP ($K=0.82$, CI 0.75–0.90). There was also very good agreement between readers for post-treatment measurements ($K=0.82$, CI 0.75–0.89 for mean tumour maximum diameter, $K=0.82$, CI 0.74–0.90 for tumour volume; $K=0.86$, CI 0.82–0.91 for HAP; $K=0.86$, CI 0.81–0.92 for PVP). ADC showed good agreement for pretreatment ($K=0.79$, CI 0.70–0.88) and post-treatment measures ($K=0.76$, CI 0.69–0.84).

Anatomical metrics

RECIST—Tumour diameter remained unchanged post-treatment, mean pretreatment and 3–4 week post-treatment tumour size measuring 8.3 cm and 8.1 cm, respectively ($p=0.44$) (Table 2). Using RECIST, no patients were classified as complete responders (CR), two (4.8 %) were PR, 37 (90.2 %) were SD and two (4.8 %) had PD (Fig. 4).

EASL and mRECIST—EASL and mRECIST obtained in the axial plane could not be used to assess tumour response in a subset of patients ($n=12$, 29 %), because on the post-treatment MR imaging there was a zone of central necrosis, with heterogeneous and rim enhancement patterns precluding accurate measurement of enhancement. Using EASL, four

(9.7 %) patients were classified as CR, 14 (34.1 %) as PR, seven (17 %) as SD and four (9.7 %) as PD. According to mRECIST, three (7.3 %) patients were classified as CR, 12 (29.2 %) as PR, ten (24.3 %) as SD and four (9.7 %) as PD.

Tumour volume—Total volume decreased minimally after treatment, from a mean of 333.4 cm³ to a 3–4-week post-treatment value of 329.8 cm³ ($p=0.86$) (Table 2).

Volumetric functional metrics

Volumetric ADC—The mean volumetric ADC increased from to 1.32×10^{-3} mm²/sec to 1.60×10^{-3} mm²/sec ($p<0.001$). The median percent volumetric ADC increased by 11.6 % post-treatment (Table 2). Treatment response as measured from the change in volumetric ADC did not predict patient survival on univariate K-M analysis (log rank, $p=0.71$) (Fig. 4b).

Volumetric enhancement in HAP—Volumetric enhancement in AE decreased from 38.2 % to 17.6 % ($p<0.001$), with a median percent decrease of 54.7 % (Table 2). Treatment response by change in volumetric enhancement in HAP did not predict patient survival on univariate K-M analysis (log rank, $p=0.58$) (Fig. 4c).

Volumetric enhancement in PVP—Volumetric enhancement in PVP decreased from 76.6 % to 41.2 % ($p<0.005$) with a median percent decrease of 54.9 % (Table 2). Patients who demonstrated 65 % decrease in enhancement in PVP had significantly improved survival compared to patients who had either a <65 % decrease or increase in volumetric enhancement (median survival of 823 vs. 372 days, log rank $p<0.005$) (Fig. 5).

In multiparametric cox regression analysis, factors that predicted patient survival after treatment with combination DEB TACE and sorafenib were a treatment response by volumetric enhancement in PVP with a hazard ratio of 3.6 (CI: 1.2–10.6, $p=0.02$) and BCLC staging with a hazard ratio of 3.5 (CI: 1.3–9.5, $p<0.01$) (Table 3).

Discussion

The assessment of tumour response using volumetric ADC and volumetric enhancement in HCC patients treated by the combination of DEB TACE and sorafenib has yet to be reported in the literature. In the prospective study of DEB TACE combined with sorafenib, the assessment of early treatment response by volumetric enhancement in the portal venous phase was able to stratify patients into responders and non-responders, with overall patient survival as the primary end point. A decrease of 65 % in volumetric enhancement in PVP had a significant impact in responders, increasing the overall median survival threefold. Response assessment by volumetric ADC and volumetric AE did not predict patient survival and failed to stratify patients treated with a combination of DEB TACE and sorafenib as responders and non-responders. EASL and mRECIST could not be utilized for response assessment in 29 % of the patients. Early treatment response assessment by RECIST did not predict patient survival in our cohort.

In the current study, volumetric enhancement in that HAP did not predict patient survival 3–4 weeks post-IAT using univariate cox proportional hazard analysis (Hazard ratio= 0.795; $p=0.727$). Our hypothesis is that our population showed considerably large tumours at presentation (9.6 ± 5.1 cm) with poor tumour enhancement on the arterial phase (mean value of 38.2 %). Despite the significant differences in tumour volumetric HAP pretreatment and post-treatment, the difference was not sufficient to achieve statistical significance on patient survival with univariate cox proportional hazard analysis. However, univariate cox proportional hazard analysis demonstrated that changes in volumetric enhancement in the PVP can predict overall patient survival (Hazard ratio= 3.569; $p=0.02$). It is likely that heterogeneous early volumetric enhancement of these large tumours in the hepatic arterial phase is limited in assessing treatment response. Increasing enhancement in the entire tumour volume in the portal venous phase may help distinguish viable from necrotic zones of the tumour. Therefore, reduction in portal venous enhancement could potentially be a better biomarker for tumour response than reduction in the arterial enhancement.

Previous results by Bonekamp et al. demonstrate treatment response evaluation by increased ADC values in patients with HCC treated only by TACE [18]. In our study, response by volumetric ADC did not predict survival in HCC patients treated by a combination of DEB TACE and sorafenib. The exact reason for this initial decrease in ADC following sorafenib treatment is not known, but could be explained either by the sorafenib-induced inhibition of angiogenesis leading to tumour ischemia, or by the presence of hemorrhagic tumour necrosis, again induced by sorafenib. Lewin et al. demonstrated that ADC and the pure diffusion coefficient did not change after treatment with sorafenib in HCC patients, although there was significant increase in perfusion fraction [26]. On the other hand, Schraml et al. showed that HCC patients treated with systemic sorafenib demonstrated an early decrease in ADC after onset of sorafenib therapy followed by an increase [27].

In this study, patients were treated with two distinct treatments—DEB TACE and sorafenib—thereby influencing ADC values. The first therapeutic component, i.e., DEB TACE, contributes to an increase in ADC, whereas the second component, i.e., sorafenib might actually decrease ADC early after treatment, as demonstrated in previous studies [27].

Changes in volumetric ADC and enhancement following IAT are dependent on the tumour histopathology. For example, in patients with intrahepatic cholangiocarcinoma treated with TACE, volumetric ADC was useful to differentiate responders from non-responders, resulting in a clear survival benefit for the responders. However, volumetric enhancement was unable to provide similar results, likely because cholangiocarcinoma is a relatively hypovascular tumour [16]. Finally, in patients with hepatocellular carcinoma and neuroendocrine tumour liver metastasis, both volumetric ADC and enhancement proved adequate in differentiating responders from non-responders, with a significant survival benefit for the responders [17, 18, 25].

Decrease in tumour size, as measured by RECIST, does not correlate well with actual tumour cell death at histopathology [28]. Changes in tumour size also tend to lag behind changes in tumour enhancement and tumour ADC, to the point that it may actually take

approximately 6 months before any change in tumour size can be used for response assessment [18, 29].

Recent clinical practice guidelines jointly issued by the EASL and the European Organization for Research and Treatment of Cancer (EASL-EORTC guidelines) state that assessment of response in HCC should be based on mRECIST by performing contrast-enhanced computed tomography or magnetic resonance imaging one month after initial treatment and at least every 3 months thereafter [30]. Although it is fairly easy to use these guidelines to measure changes in tumour enhancement in the axial plane after treatment, such measurements may not be accurate, since they may not be representative of the entire tumour volume.

It is well known that determining early response to locoregional therapy for liver cancer is critically important. Patients who respond well after an initial session of IAT could forego another session to avoid unnecessary toxicity, whereas those who did not respond well to the first session could indeed benefit from another session [31], or could potentially be considered for other types of IAT.

The first ten cases were reviewed by two independent reviewers, and the differences in parameters measured were not statistically significant. Inter-reader agreement of functional (ADC, HAP and PVP) volumetric and morphological MRI (tumour volume, RECIST and EASL) for the assessment of response to treatment in patients with HCC has been addressed in detail in a previous study [32]. Results from that study showed that semi-automated volumetric measurements of functional parameters (ICC=0.83–0.974), tumour volume (ICC=0.854–0.996) and size in the axial plane before and after IAT had good to excellent inter-observer agreement compared with manual ROI-based axial measurements (ICC=0.157–0.799 and ICC=0.543–0.596, respectively). Bonekamp et al. [32] concluded that semi-automated measurement of functional changes assessed by ADC and PVP based on whole-lesion demonstrated better reproducibility than ROI-based axial measurements of RECIST or EASL.

Our study comes with limitations. First, we did not obtain histopathological confirmation of tumour necrosis. However, we utilized overall patient survival as our primary endpoint. Another limitation is that we used only the index lesion, i.e., the largest treated lesion in the first session of IAT, for response assessment. Yet, in some patients with high tumour burden, the entire tumour volume could have been utilized. Our rationale for using the primary index lesion is similar to that of a prior study by Rias et al. [33], which reported that changes in the primary index lesion could be biomarkers of treatment response.

In conclusion, results from our prospective study show that changes in volumetric enhancement in the PVP demonstrated significant survival differences between responders (≥ 65 % decrease in PVP) and non-responders (<65 % decrease or increase in PVP). We therefore postulate that volumetric tumour assessment in the PVP could be used to quantify early treatment response after the combination of DEB TACE and sorafenib.

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Abbreviations

HCC	Hepatocellular carcinoma
IAT	Intra-arterial therapies
DEB	Doxorubicin-eluting bead–transarterial
TACE	chemoembolization
RECIST	Response evaluation criteria in solid tumours
mRECIST	Modified RECIST
EASL	European association for study of liver disease
ADC	Apparent diffusion coefficient
DWI	Diffusion weighted imaging
MRI	Magnetic resonance imaging
CE-MRI	Contrast enhanced MRI
HAP	Hepatic arterial phase
PVP	Portal venous phase
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
K-M	Kaplan Meier
AFP	Alpha fetoprotein
BCLC	Barcelona clinic liver cancer
ECOG	Eastern cooperative oncology group

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Key Points

- PVP enhancement is significantly correlated with survival in responders ($p<0.005$).
- There was no significant survival difference for early response using RECIST ($p=0.93$).
- mRECIST or EASL could not assess tumour response in 29 % of patients.

Fig. 1.

Inclusion and exclusion criteria in our patient population

Fig. 2.

Hepatocellular carcinoma pretreatment and post-treatment showing volumetric change by PVP. Hepatocellular carcinoma (a) at baseline showed a tumour volume of 294.3 cm³, while (b) Post-treatment tumour volume was 266.6 cm³. The lesion showed no change by RECIST. c Volumetric ADC map showed no change in mean volumetric ADC from 1.23×10^{-3} mm²/sec before treatment to 1.35×10^{-3} mm²/sec after treatment, as depicted in the histogram (blue: pretreatment, orange: post-treatment). d Enhancement in HAP decreased from 24.7 % to 2.2 % post-treatment, as depicted in the histogram (blue: pretreatment, orange: post-treatment). e Histogram depicts that enhancement in PVP decreased from 73.6 % to 24.3 %, with a 66 % decrease early post-treatment (blue: pretreatment, orange: post-treatment). There is a leftward shift in the blended histogram representing decreasing enhancement post-treatment and indicating favorable response to therapy

Fig. 3.

Hepatocellular carcinoma assessed pretreatment and post-treatment by volumetric functional MRI. Hepatocellular carcinoma **(a)** at baseline showed a tumour volume of 333.8 cm³, while **(b)** Post treatment tumour volume was 255.8 cm³. **c** Volumetric ADC map showed volumetric mean ADC change from 1.64×10^{-3} mm²/sec to 1.55×10^{-3} mm²/sec as depicted in the histogram (*blue*: pretreatment, *orange*: post-treatment). **d** Enhancement in HAP increased from 1.33 % to 46.9 % post-treatment, as depicted in the histogram (*blue*: pretreatment, *orange*: post-treatment). **e** Enhancement in PVP increased from 73.9 % to 100 % after treatment, as depicted in the histogram (*blue*: pretreatment, *orange*: post-treatment)

Fig. 4.

Survival in months, stratified by RECIST, volumetric ADC and enhancement in arterial phase in responders and non-responder 3–4 weeks after treatment. **a** The *blue curve* represents responders by RECIST ($n=2$, median survival of 502 days) and the *green curve* represents non-responders by RECIST ($n=39$, median survival of 563 days) 3–4 weeks post-treatment with combination DEB TACE and Sorafenib. [log rank $p=0.93$]. **b** The *blue curve* represents responders ($<25\%$ decrease in ADC, $n=11$, median survival of 563 days) and the *green curve* represents non-responders ($<25\%$ decrease or increase in ADC, $n=23$, median survival of 686 days) 3–4 weeks post-treatment with combination DEB TACE and Sorafenib [log rank $p=0.71$]. **c** The *blue curve* represents responders ($<50\%$ decrease in HAP, $n=22$, median survival of 631 days) and the *green curve* represents non-responders ($<50\%$ decrease or increase in HAP, $n=19$, median survival of 404 days) 3–4 weeks post-treatment with combination DEB TACE and Sorafenib [log rank $p=0.58$]

Fig. 5.

Survival in months stratified by volumetric enhancement in portal venous phase, stratifying responders from non-responder 3–4 weeks after treatment. The *blue curve* represents responders ($\geq 65\%$ decrease in PVP, $n=19$, median survival of 823 days) and the *green curve* represents non-responders ($<65\%$ decrease or increase in PVP, $n=22$, median survival of 372 days) 3–4 weeks post-treatment with combination DEB TACE and Sorafenib [log rank $p<0.005$]

Table 1

Tumour response assessment according to RECIST, mRECIST and EASL

Response category	RECIST	mRECIST	EASL
Complete response	100 % decrease in maximum diameter of target lesion	100 % decrease in maximum enhancing diameter	100 % decrease of enhancing tissue of target lesion
Partial response	30 % decrease of longest diameter	30 % decrease of longest enhancing diameter	50 % decrease bi-dimensional enhancing are of tumour
Stable disease	<30 % decrease or 20 % increase in lesion size	<30 % decrease to 20 % increase in enhancing tissue	<50 % decrease to 25 % increase in enhancing tissue
Progression of disease	Increase of >20 % in lesion size or new lesions	>20 % increase of maximum enhancing diameter or new enhancing lesion	>25 % increase of enhancing tissue or new enhancing lesion

RECIST Response Evaluation Criteria in Solid Tumours; *mRECIST* modified RECIST; *EASL* European Association for Study of the Liver

Table 2

Paired *t*-test for comparison of MR imaging variables in our cohort of 41 patients pretreatment and post-treatment, as measured by Reader 2

	Pretreatment	Post-treatment	<i>p</i> value	Median percent change
RECIST (cm)	8.3±4.1	8.1±4.3	0.44	0.00
Total Diameter (cm)	9.6±5.1	9.4±5.5	0.62	-1.2
Tumour Volume (cm ³)	333.4	329.8	0.86	-5.2
Volumetric ADC (x 10 ⁻³ mm ² /sec)	1.32±0.2	1.60±0.4	< 0.001	11.6
Volumetric enhancement in arterial phase (%)	38.2±32.1	17.6±22.6	< 0.001	-54.7
Volumetric enhancement in portal venous phase (%)	76.6±31.1	41.2±34.9	< 0.005	-54.9

Table 3

Multivariate cox proportional hazard model

	Hazard ratio	95 % CI lower - higher	p value
RECIST	2.0	0.2–20.1	0.56
Volumetric ADC	0.6	0.2–2.1	0.45
Volumetric enhancement in arterial phase	0.8	0.2–2.9	0.73
Volumetric enhancement in portal venous phase	3.6	1.2–10.6	0.02
BCLC	3.5	1.3–9.5	<0.01
ECOG status	1.2	0.4–3.3	0.71
Age	1.0	1.0–1.1	0.61