Quantitative volumetric functional MR imaging: an imaging biomarker of early treatment response in hypo-vascular liver metastasis patients after yttrium-90 transarterial radioembolization

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Abstract

Purpose: To evaluate the value of quantitative volumetric functional MR imaging in early assessment of response to yttrium-90-labeled (^{90}Y) transarterial radioembolization (TARE) in patients with hypo-vascular liver metastases.
Materials and methods: Seventy four metastatic lesions in 14 patients with hypo-vascular liver metastases after TARE were included in this retrospective study. Diffusion and contrast-enhanced MR imaging was performed before and early after treatment. All MR images were analyzed by two experienced radiologists. Response by anatomic metrics (RECIST, mRECIST, EASL) and functional metrics (ADC and arterial and venous enhancement) were reported in targeted and non-targeted lesions. A two-sample paired *t* test was used to compare the changes after TARE. A *p* value of <0.05 was considered statistically significant.
Results: The anatomic metrics did not show any significant changes in both targeted and non-targeted groups. Targeted lesions demonstrated an increase in mean volumetric ADC (23.4%; *p* = 0.01), a decrease in arterial and venous enhancement (−22.9% and −6.7%, respectively; *p* < 0.001 and *p* = 0.002, respectively) 1 month after treatment. Twenty one responding lesions (42%) by RECIST at 6 months demonstrated a significant increase

in volumetric ADC (37.2%; *p* = 0.01), decrease in arterial and venous enhancement (−58.5% and −23.9%, respectively; *p* < 0.001) at 1 month post-treatment. Responding lesions did not change significantly by anatomic metrics.
Conclusions: RECIST, mRECIST, and EASL criteria failed to stratify lesions into responders and non-responders early after TARE in hypo-vascular liver metastasis. Quantitative volumetric functional MR imaging could be a promising tool as a biomarker for predicting early response and can potentially be utilized in clinical trials.

Abbreviations

TARE	Transarterial radioembolization
^{90}Y	Yttrium-90
RECIST	Response evaluation criteria in solid tumors
EASL	European association for the study of the liver
HCC	Hepatocellular carcinoma
mRECIST	Modified RECIST
MRI	Magnetic resonance imaging
DWI	Diffusion-weighted imaging

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ADC	Apparent diffusion coefficient
LRT	Loco-regional therapy
NELM	Neuroendocrine liver metastases
ICLM	Islet cell liver metastases
TACE	Transarterial chemoembolization
HAE	Hepatic arterial enhancement
PVE	Portal venous enhancement
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progression of disease

The liver is a common site for primary and secondary malignancies. Hepatic metastases are found in 40% of all patients diagnosed with cancer [1]. Autopsy studies have demonstrated that the liver is involved in 50% to 70% of metastases from melanoma, lymphoma, and common malignancies that originate in the breast, lung, and gastrointestinal tract. Based on their blood supply, metastases may be categorized as hyper-vascular and hypo-vascular. Colon, breast, lung, and gastric carcinomas are the most common tumors causing hypo-vascular liver metastases, which typically show minimal rim or perilesional enhancement [2]. Although surgical resection is the only curative therapeutic option for secondary hepatic malignancies, most patients are often poor candidates for this treatment because of several factors including poor hepatic reserve, the presence of numerous bilobar tumors or extrahepatic disease. For those patients, intraarterial therapy is becoming an essential therapeutic option [3].

Offering a minimally invasive treatment pathway with promising clinical results, transarterial radioembolization (TARE) with Yttrium-90 (^{90}Y) microspheres is a catheter-based, liver-directed therapy that is now available for the treatment of primary and metastatic liver malignancy ineligible to undergo surgery [4–8]. Delivered intraarterially through a catheter placed in the hepatic artery feeding the tumors, the microspheres provide a lethal radiation dose to tumor cells, destroying vascular flow and resulting in cellular death and tumor necrosis [9], with low toxicity to normal liver and minimal side effects.

Precise and early assessments of treatment response after ^{90}Y microsphere is critical not only to evaluate the therapeutic effect, but also to determine whether repeated treatment is needed [10]. Current traditional and accepted anatomic imaging criteria for evaluating tumor response include response evaluation criteria in solid tumors (RECIST), which requires uni-dimensional measurement of the entire lesion in an axial plane. The European association for the study of the liver (EASL) proposed the estimation of reduction in viable tumor area bi-dimensionally [4]. More recently, modified RE-CIST (mRECIST) was proposed, and is based on reduction of the longest diameter of enhancing tumor in the axial plane. Measuring the residual enhancing tissue by EASL and mRECIST criteria was intended to predict treatment response of hyper-vascular tumors, particularly hepatocellular carcinoma (HCC). The utility of these anatomic metrics in assessing response of hypo-vascular metastases to TARE is not well evaluated.

The recent development of novel functional magnetic resonance (MR) imaging techniques provided objective, quantitative evaluation of tissue perfusion and cellular integrity. Diffusion-weighted imaging (DWI) and the quantifiable apparent diffusion coefficient (ADC) detect motion of water within tumor tissues, which has been useful in tumor detection, characterization, and in monitoring response to treatment [11–13]. Previous studies have demonstrated that volumetric functional MR imaging can help in accurately assessing tumor response after loco-regional therapy (LRT) in patients with HCC, neuroendocrine liver metastases (NELM), and islet cell liver metastases (ICLM) [14–16]. The objective of this study was to assess the value of quantitative volumetric biomarkers to evaluate early (1 month) response after ^{90}Y-radioembolization in hypo-vascular liver metastasis, and compare those metrics to current metrics including RECIST, mRECIST, and EASL.

Materials and methods

This single-institute retrospective study was performed in compliance with the Health Insurance Portability and Accountability Act (HIPAA) after obtaining a waiver for informed consent approved by our institutional review board (IRB).

Study population

We reviewed a database of patients with hypo-vascular metastatic liver tumors with absent or limited extrahepatic disease who underwent first line LRT from January 2008 to March 2015 at our Institution. All patients enrolled had hypo-vascular liver metastases by MRI described as hypo-intense appearance compared to the enhancing normal liver parenchyma with perilesional enhancement. Inclusion criteria for enrollment were (a) patients who received a clinical confirmed diagnosis of liver metastases from a primary malignancy; (b) patients who have undergone ^{90}Y microsphere treatment at our institution; and (c) patients who underwent MR imaging with DWI and contrast-enhanced MR imaging at baseline, 1 and 6 months after treatment. Of 44 patients who had hypo-vascular liver metastases, we excluded 27 patients who undergone TACE treatment, and 3 patients for the absence of MR images before or after treatment. The remaining 14 patients were included in this retrospective study (Fig. 1).
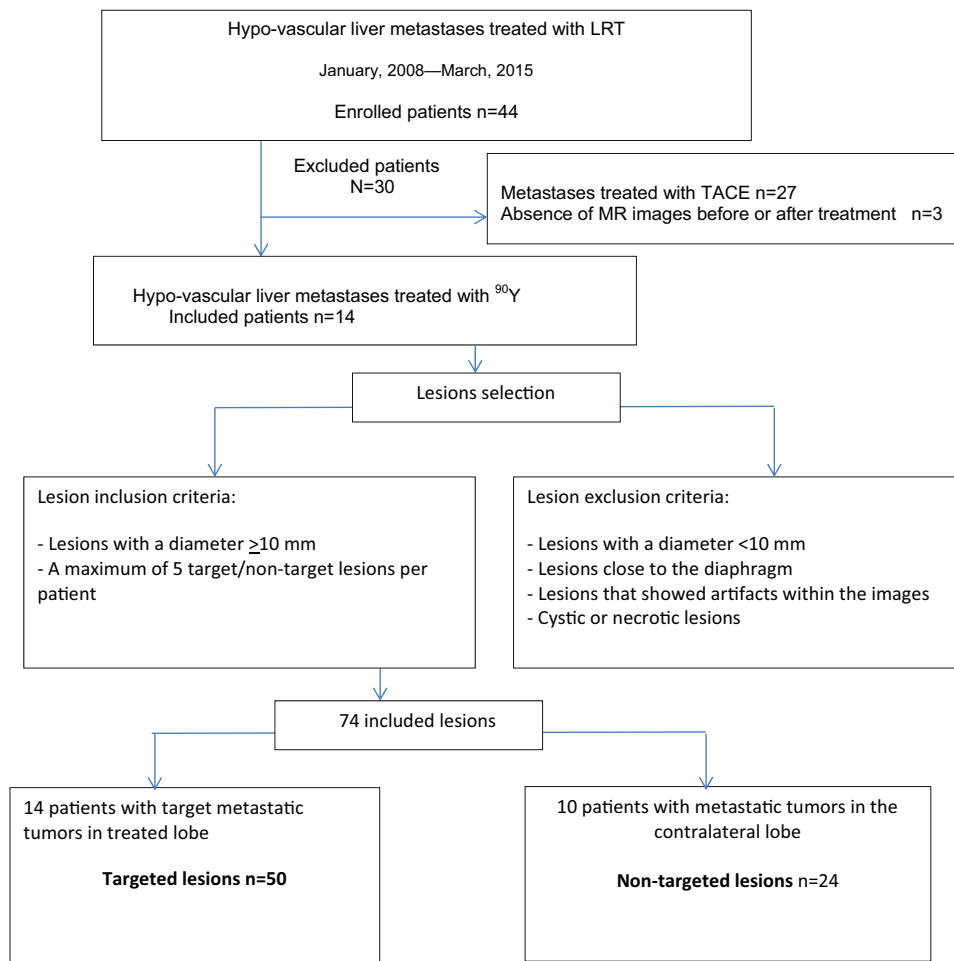
Fig. 1. Study design flow chart.

^{90}Y microsphere treatment

^{90}Y is a beta radiation emitter with half-life of 64.2 h and an average energy of 0.94 MeV. The radiation had a mean tissue penetration of 2.5 mm, and 94% of the dose is delivered within the first 11 days following administration of TheraSpheres (BTG International Canada Inc, Ottawa, ON, Canada). TheraSpheres are made of glass and ^{90}Y is embedded within the glass matrix leading to higher density and specific activity (2500 Bq) of the preparation [9].

All procedures were performed by an experienced multidisciplinary team including board-certified interventional radiologists. A week before treatment, each patient underwent an angiogram to map the anatomy of the hepatic arterial system and protectively embolized vessels permitting microspheres to enter the GI tract. The liver volume treated was determined by MRI with a conversion factor of 1.03 g/cm^3, the corresponding liver mass was determined. A technetium-99 (^{99}Tc) macroaggregated albumin scan was performed to observe if there was gastrointestinal flow and to determine the percent of injected activity shunted to the lungs. According to individual patient clinical demand, the elective segmental or lobar TARE was injected into the hepatic artery feeding the tumor. Patients were monitored for 2 h after the procedure and were subsequently discharged [17, 18].

MR imaging technique and parameters

All 14 patients underwent MR scan at baseline and follow-up at 1 and 6 months after TARE. MRI was performed with a 1.5 T whole-body MR (Magnetom Avanto; Siemens Healthcare, Erlangen, Germany) unit using a phased array torso coil. The imaging protocol included axial T2-weighted fast spin-echo (FSE) navigation MR imaging (TR/TE 4500/92 ms; 256 × 256 matrix; 8-mm-thick slice; 2 mm gap; 32 Hz/pixel bandwidth); axial breath-hold single-shot echo-planar (SE-EPI) DWI (TR/TE 3000/69 ms, 128 × 128 matrix, 380 mm field of view, 8-mm-thick slice, 2 mm gap, b values of 0 and 750 mm^2/s, 64 Hz/pixel bandwidth) with fat suppression; and axial breath-hold unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadopentetate dimeglumine, Magnevist; Bayer, NJ) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo (GRE) imaging (TR/TE 5.77/2.77 ms, 400 mm field of

Table 1. The sequence and parameters of the MR imaging Acquisition

Parameter	FSE-T2WI	SE-EPI DWI	3D FS GRE T1WI
TR/TE	4500/92	3000/69	5.77/2.77
Matrix	256×256	128×128	192×160
FOV (mm)	380	380	400
Thickness (mm)	8	8	2.5
Intersection gap (mm)	2	2	64
Bandwidth	32	1346	–
b values (mm^2/s)	–	0, 750	–

FSE, fast spin-echo; *WI*, weighted images; *SE-EPI*, single-shot echo-planar images; *DWI*, diffusion-weighted imaging; *FS*, fat saturation; *GRE*, spoiled gradient-echo

view, 192×160 matrix, 2.5 mm slice thickness, 64 Hz/pixel bandwidth, 10° flip angle) in hepatic arterial phase (20 s) and portal venous phases (70 s) (Table 1).

MR image analysis

All MR images were evaluated by consensus of two experienced radiologists. Up to 5 hypo-vascular metastatic lesions were selected with a diameter ≥10 mm per patient in both targeted and non-targeted lobes to ensure independent sampling. Smaller (<10 mm) lesions were not included due to difficulty in measuring ADC values of these lesions. Also, lesions close to the diaphragm were excluded to avoid breathing artifacts (Fig. 1).

A total of 50 targeted and 24 non-targeted lesions were analyzed at baseline and 1 month post-treatment according to (a) RECIST, (b) mRECIST, (c) EASL criteria, (d) volumetric ADC, and (e) volumetric HAE and PVE. Conventional anatomical metrics, including RECIST, mRECIST, and EASL were measured in portal venous phase using Emageon Ultravisual (Medical Systems Corporation, Birmingham, AL) software. Volumetric ADC and enhancement analysis was performed using proprietary software (MR Oncotreat, Siemens Healthcare, Princeton, USA). In the first step, patient DICOM data were imported into the software and registered for calculation; secondly, tumor borders were defined with an interactive segmentation technique that was previously described [19]. Percent change in volumetric tumor ADC and enhancement at 1 month follow-up compared with baseline values was calculated using the following formula: $\frac{T_{post} - T_{pre}}{T_{pre}} \times 100$, where T_{pre} is vol-

umetric ADC or enhancement before treatment and T_{post} is volumetric ADC or enhancement 1 month after TARE.

Study endpoint

RECIST at 6 months after initial TARE was our endpoint for each lesion. Fifty targeted lesions were stratified into responders [including complete response (CR) and partial response (PR)] and non-responders [including stable disease (SD) or progressive disease (PD)], as defined in Table 2.

Statistical analysis

A two-sample paired t test was used to determine if comparison between anatomic and volumetric functional MR metrics at baseline and 1 month after TARE were significantly different for all targeted and non-targeted lesions, including tumor size by RECIST, tumor enhancement by mRECIST, tumor enhancement by EASL, volumetric HAE, volumetric PVE, and volumetric ADC. Similar comparisons were also made for responders and non-responders. Statistical analysis was performed with a software package (SPSS, version 16.0; SPSS, Chicago, IL). A p value of <0.05 was considered significant.

Results

Demographic information

Demographic information of the 14 patients (mean age 60 ± 13 years; range between 33 and 86 years) in our

Table 2. Response evaluation criteria

	RECIST	mRECIST	EASL
Complete response (CR)	100% decrease in maximum diameter of target lesion	100% decrease in maximum enhancing diameter	100% decrease of enhancing tissue of target lesion
Partial response (PR)	≥30% decrease of longest diameter	≥30% decrease of longest enhancing diameter	≥50% decrease bi-dimensional enhancing are of tumor
Stable disease (SD)	<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 (PD)	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 tumor; *mRECIST*, modified response evaluation criteria in solid tumor; *EASL*, European association for the study of liver disease

study is summarized in Table 3. A total of 50 targeted and 24 non-targeted lesions were analyzed. The majority of patients included were Caucasian (43%) and females (86%).

^{90}Y microsphere treatment

All 14 patients successfully completed ^{90}Y microsphere radioembolization treatment without immediate (within 24 h) complications. Five patients underwent TARE once, 8 patients underwent TARE twice, and 1 patient underwent TARE three times (mean 1.7 ± 0.6, range 1–3). Nine patients received TARE in both lobes, 4 patients to the right lobe, and 1 patient to the left lobe.

Table 3. Demographics data

Characteristics	Mean ± standard deviation
Age (years old)	
All patients	60 ± 13
M	57 ± 2
F	61 ± 14
Gender	
M	2 (14)
F	12 (86)
M/F	1:6
Ethnicity	
White	8 (43)
African American	4 (43)
Other	2 (14)
Primary malignancies	
Breast cancer	6 (43)
Colorectal cancer	8 (57)
Times of treatment	
One session	5 patients
Two sessions	8 patients
Three sessions	1 patients
Liver lobe treated	
Right liver lobe	4
Left liver lobe	1
Whole liver in two sessions	9

Numbers in parenthesis are percentages
F, female; *M*, male

MR imaging findings

The mean number of lesions for the 14 patients was 3.5. The mean pretreatment diameter was 2.9 ± 2.4 and 2.6 ± 1.3 cm for the targeted and non-targeted lesions, respectively.

Anatomic and volumetric functional metrics at baseline and 1 month post-treatment in targeted lesions
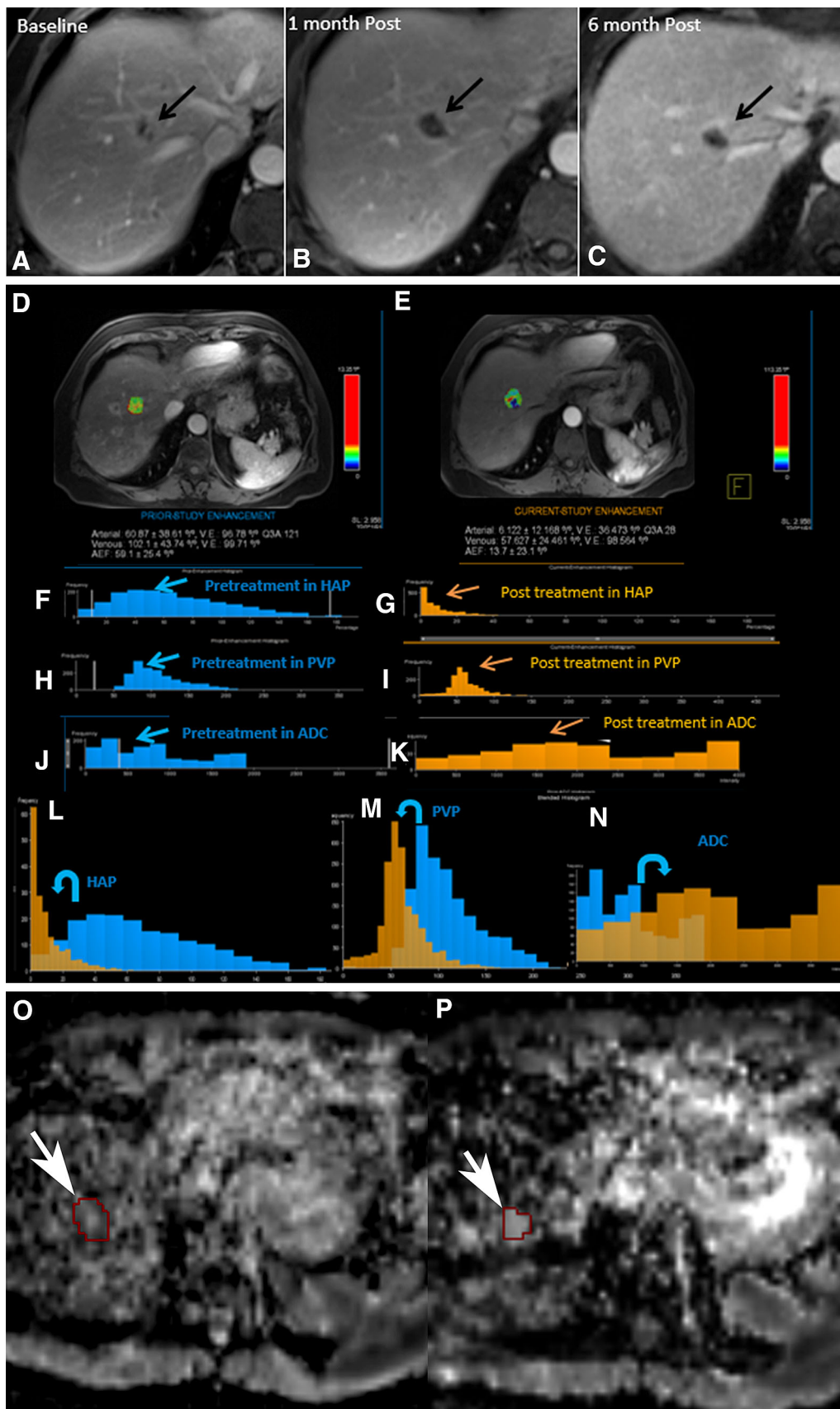
Table 4 shows anatomic and volumetric measurements for the targeted lesions at baseline and 1 month after treatment. Targeted lesions did not change significantly in size by RECIST ($p = 0.74$), mRECIST ($p = 0.31$), nor EASL ($p = 0.23$). Targeted tumors demonstrated a significant decrease in mean HAE of 22.9% ($p < 0.001$), a decrease in mean PVE of 6.7% ($p = 0.002$), and a significant increase in mean ADC value of 23.4% ($p = 0.01$) (Fig. 2).

Anatomic and volumetric functional metrics at baseline and 1 month post-treatment in non-targeted lesions

Table 5 shows anatomic and volumetric measurements for the non-targeted lesions at baseline and 1 month after treatment. Similar to targeted metastasis, non-targeted lesions did not change significantly in size by RECIST ($p = 0.17$), mRECIST ($p = 0.30$), nor EASL ($p = 0.47$). Also, functional volumetric measures of non-targeted lesions did not show significant changes by mean HAE ($p = 0.30$), mean PVE ($p = 0.88$), or mean ADC value ($p = 0.72$) after treatment.

Stratification of targeted lesions by RECIST response at 6-month follow-up

In accordance to RECIST guidelines at 6-month follow-up, the targeted lesions were stratified into 21 (42%)

Table 4. Changes in anatomical metrics and volumetric functional metrics before and early (1 month) after TARE for targeted lesions ($N = 50$)

$n = 50$	Baseline	1 Month after treatment	Mean percentage change	p value
Anatomical metrics				
RECIST (cm)	2.9 ± 2.4	2.9 ± 2.5	1.2	0.74
mRECIST (cm)	2.8 ± 2.3	2.7 ± 2.3	−3.3	0.31
EASL (cm^2)	9.3 ± 26.3	8.7 ± 24.7	−7.0	0.23
Volumetric metrics				
HAP (%)	56.1 ± 33.8	31.7 ± 25.7	−22.9	<0.0001
PVP (%)	85.5 ± 26.8	72.3 ± 25.5	−6.7	0.002
ADC ($\times 10^{-3}$ mm^2/s)	1.1 ± 0.4	1.3 ± 0.6	23.4	0.01

Values are expressed as means ± standard deviations
* p value is obtained from independent-samples t test
RECIST, response evaluation criteria in solid tumor; *mRECIST*, modified RECIST; *EASL*, European Association for the Study of Liver Disease; *HAP*, hepatic arterial phase; *PVP*, portal venous phase

Anatomic metrics in a 60-year-old female diagnosed with breast cancer liver metastases. RECIST was measured in an axial plane in portal venous phase images at baseline (**A**), 1 month (**B**), and 6 months (**C**) post-treatment (*arrows*). The maximum diameter of the lesion did not show any changes in size, the lesion measured 1.52 cm at baseline and at 6 month follow-up. The lesions were categorized as SD by RECIST. Volumetric metrics of the tumor at baseline (**D**) and 1 month after treatment (**E**) in the same lesion. Enhancement in the hepatic arterial phase decreased from 60.9% (**F**) to 6.1% (**G**), showing a 90% decreased enhancement. Portal venous phase enhancement decreased from 100% (**H**) to 57.6% (**I**), demonstrating a 46.6% decreased enhancement. ADC changed from 0.75×10^{-3} mm^2/s (**J**) to 2.64×10^{-3} mm^2/s (**K**), increasing by 254%. The histogram (*blue* = pretreatment data, *orange* = post-treatment data) showed favorable response with leftward shift in the hepatic arterial (**L**) and portal venous (**M**) phases, and rightward shift in ADC (**N**). ADC images before (**O**) and after (**P**) therapy are also shown.

responders [CR 10% ($n = 5$); PR 32% ($n = 16$)] and 29 (58%) non-responders [SD 44% ($n = 22$); PD 14% ($n = 7$)].

Anatomic and volumetric functional metrics at 1 month post-treatment in targeted lesions

Table 6 shows anatomic and volumetric measurements for the 21 responders and 29 non-responders at baseline and 1 month after treatment. Responders did not change significantly in size by RECIST ($p = 0.08$), mRECIST ($p = 0.08$), nor EASL ($p = 0.06$). Responders demonstrated a significant decrease in mean HAE of 58.5% ($p < 0.001$), a significant decrease in mean PVE of 23.9% ($p < 0.001$), and a significant increase in mean ADC value of 37.2% ($p = 0.01$). Moreover, non-responders did not change significantly in size by RECIST ($p = 0.08$), mRECIST ($p = 0.72$), nor EASL ($p = 0.90$). Non-responders also did not show significant changes in mean HAE (increased by 2.9%,

$p = 0.10$), mean PVE of (increased by 5.7%, $p = 0.37$), and ADC value of (increased by 7.4%, $p = 0.31$).

Discussion

To our knowledge, the value of quantitative volumetric functional MRI in predicting early treatment response of hypo-vascular hepatic metastasis has not been established to date. This retrospective study identified the potential value of quantitative volumetric functional MRI by ADC, HAE, and PVE to predict early (1 month) response to ⁹⁰Y-radioembolization in hypo-vascular liver metastasis. Furthermore, anatomic methods (RECIST, m RECIST, EASL) failed to stratify lesions according to tumor response early after therapy.

⁹⁰Y microspheres obliterate tumor vascular flow and result in cellular death and tumor necrosis, affecting the functional and physiologic behavior of the lesion more than the tumor size. Traditional anatomic criteria based on decrease in tumor size in the axial plane show significant limitation in detecting early tumor response to TARE therapy [18, 20]. While tumor shrinkage may not be initially apparent, there were changes in tumor ADC and enhancement that could be valuable in assessing early therapeutic efficacy [21–23]. Previous studies [4, 15, 24] demonstrated the promising role of quantitative volumetric functional MRI to detect early tumor response to LRT of liver malignancies. Changes in volumetric functional MR metrics may precede conventional tumor size changes, potentially overcoming the limitations of mRECIST and EASL.

Our study demonstrated statistically significant changes in functional MRI metrics (ADC, HAE, and PVE) early (1 month) after treatment in all 50 targeted lesions (Table 4). The anatomic metrics did not show any significant changes in both, the targeted and the non-targeted groups (Table 5). This finding is particularly important not only to evaluate the therapy effect, but also to determine whether repeated treatment is needed before disease progression is seen by anatomical metrics.

Table 5. Comparison in anatomic metrics and volumetric functional metrics before and early (1 month) after TARE between targeted ($n = 50$) and non-targeted lesions ($n = 24$)

	Targeted $n = 50$				Non-targeted $n = 24$			
	Baseline	1 Month after treatment	Mean percentage change	p value	Baseline	1 month after treatment	Mean percentage change (%)	p value*
Anatomical metrics								
RECIST (cm)	2.9 ± 2.4	2.9 ± 2.5	1.2	0.74	2.62 ± 1.3	2.80 ± 1.58	7.2	0.17
mRECIST (cm)	2.8 ± 2.3	2.7 ± 2.3	−3.3	0.31	2.59 ± 1.4	2.72 ± 1.61	4.4	0.30
EASL (cm^2)	9.3 ± 26.3	8.7 ± 24.7	−7.6	0.23	6.29 ± 6.5	6.94 ± 0.24	6.1	0.47
Volumetric metrics								
HAP (%)	56.1 ± 33.8	31.7 ± 25.7	−22.9	0.00003	48.7 ± 25.7	42.3 ± 25.9	3.0	0.30
PVP (%)	85.5 ± 26.8	72.3 ± 25.5	−6.7	0.002	72.5 ± 24.5	73.1 ± 23.2	6.2	0.88
ADC ($\times 10^{-3}$ mm^2/s)	1.12 ± 0.4	1.3 ± 0.6	23.4	0.01	1.2 ± 0.5	1.2 ± 0.5	10.0	0.72

* p value is obtained from independent-samples t test

Table 6. Changes in anatomical and volumetric functional metrics before and early (1 month) after TARE according to response by RECIST at 6 months

	Responders $n = 21$				Non-responders $n = 29$			
	Baseline	1 month after treatment	Mean percentage change	p value	Baseline	1 month after treatment	Mean percentage change (%)	p value*
Anatomical metrics								
RECIST (cm)	2.6 ± 1.7	2.2 ± 1.1	-5.5	0.083	3.2 ± 2.8	3.4 ± 3.1	6.1	0.08
mRECIST (cm)	2.4 ± 1.4	2.2 ± 1.1	-4.5	0.080	3.1 ± 2.8	3.1 ± 2.8	-2.3	0.72
EASL (cm^2)	5.6 ± 8.4	4.2 ± 5.7	-10.3	0.057	12.0 ± 33.8	11.9 ± 32.0	-4.5	0.90
Volumetric metrics								
HAP (%)	74.1 ± 33.7	28.6 ± 28.1	-58.5	<0.001	42.1 ± 27.7	33.9 ± 22.8	2.9	0.10
PVP (%)	96.5 ± 20.9	72.6 ± 20.9	-23.9	<0.001	77.5 ± 28.2	72.0 ± 28.8	5.7	0.37
ADC ($\times 10^{-3}$ mm^2/s)	1.1 ± 0.4	1.5 ± 0.6	37.2	0.01	1.2 ± 0.36	1.2 ± 0.5	7.4	0.31

Values are expressed as means ± standard deviations
RECIST, response evaluation criteria in solid tumor; *mRECIST*, modified RECIST; *EASL*, European Association for the Study of Liver Disease; *HAP*, hepatic arterial phase; *PVP*, portal venous phase
* p value is obtained from independent-samples t test

Volumetric functional MR metrics provide accurate and objective assessment of early treatment response after ^{90}Y microsphere, and could potentially be valuable in the clinical management of patients for prediction of therapeutic effect and in guiding future therapy [20]. Early responders by functional MR metrics may not require additional therapy unless disease progression is confirmed at follow-up imaging.

Our study also showed statistically significant changes in volumetric functional MRI metrics early (1 month) after treatment in 21 (42%) responders. For all responders, volumetric HAE and PVE decreased significantly (58.5% and 23.9% respectively), and volumetric ADC increased by 37.2% 1 month after TARE. On the contrary, anatomic metrics did not show any significant change in the responders or non-responders after therapy. Our results suggest that these potential novel functional MRI techniques can stratify patients as responders and non-responders early (1 month) after TARE, even before changes in tumor size and/or morphologic characteristics occur [16, 25].

Response by conventional size measurements may take several months to document after TARE. Miller et al. [26] showed that the traditional criteria based on size would incorrectly classify responders as progressive disease on early post ^{90}Y therapy imaging studies for liver metastasis. The measurement of tumor size could be misleading due to hemorrhage and peripheral edema to the treated lesion, which limit the use of RECIST in assessing early response after TARE. EASL and mRECIST criteria were thought to take into account the amount of cellular necrosis using changes in arterial enhancement in the axial plane as a metric of response, which were proposed to measure treatment response to hyper-vascular tumors. All subjects included in our study had hypo-vascular liver metastasis, which are often poorly defined and therefore more difficult to measure accurately due to their minimal rim or perilesional enhancement. In addition, the expected veno-occlusive changes and inflammatory reaction around the targeted lesions after TARE may cause abnormal enhancements which lead to underestimation of the tumor response. Our results are in agreement with a previous study [27] that reported poor correlation between response to LRT achieved by RECIST and EASL for liver metastasis from primary breast cancer. Our study indicates that volumetric ADC, HAE, and PVE can predict the success of the therapy before the conventional axial size measurement in patients with hypo-vascular liver metastases at a functional and molecular level. The combination of different functional MR parameters (ADC, HAE, and PVE) will also help to understand the tumor biology and to better characterize and stage tumors for treatment planning. As a non-invasive biomarkers of early treatment response with hypo-vascular liver metastases, volumetric functional MR metrics can be used to determine whether treatment is effective, which would allow clinicians to optimize individual patient treatment and avoid unnecessary systemic toxicity, expense, and treatment delays.

Our study utilized advanced yet simple and relatively fast software that allows for semi-automated segmentation of the tumor, generating metrics of cellular and molecular changes within the entire tumor volume rather than using ROI measurements in a single axial plain. Tumor necrosis after TARE occurs centrally, and therefore, 3D assessment is more representative of the changes that occur globally within a targeted lesion. Furthermore, the software enabled easy and better reproducibility analysis of multiparametric MR imaging data compared to ROI-based axial measurements [15, 24, 28]. The presented data by Chapiro et al. [29] provided multilayer proof of the precision of 3D quantitative perfusion and diffusion-weighted MR imaging when correlated with pathologic examination as a standard of Ref. [14–16]. Our data demonstrated that volumetric analysis of functional MR imaging during the hepatic arterial and portal venous phase is superior because it

takes into account the enhancement of the entire volume of the tumor.

There were several limitations to this study. This is a single-institution retrospective study that included patients with different hypo-vascular metastases who were treated with TARE. This may have resulted in selection bias. Second, our study population was relatively small; and assessing response in each individual tumor type could result in decreasing sample size. Larger sample size study is required to confirm our findings. Third, our study lacks histopathologic correlation of the lesions after ^{90}Y microsphere treatment. Histopathological proof of tumor necrosis after treatment was not feasible nor clinically indicated because of the invasive nature of the procedure, especially in terminal patients with impaired liver function. In the current study, only 2 b values were acquired for DWI. While the acquisition of additional b values may increase the accuracy of ADC calculations, the addition of b values increases sequence acquisition time which could potentially increase the MR imaging exam time. Since quantifying the change in ADC value after therapy rather than the absolute ADC value was the primary objective of this study, and to avoid increase in exam time, we opt to use the 2 b values of 0 and 750 mm^2/s. Finally, there may have been some selection bias. Only lesions ≥10 mm were selected for analysis because ADC cannot be accurately measured in smaller lesions.

Conclusions

Quantitative volumetric functional MR imaging can provide an insight into changes at cellular level before tumor size changed, which could be a promising tool in predicting and monitoring the early response to ^{90}Y microsphere treatment of the hypo-vascular liver metastasis as a biomarker. This non-invasive method could benefit the evaluation of early tumor response in future research and clinical trials.

Conflict of interest   None of the authors listed (Xiangyu Zhu, Fatemeh Sobhani, Chunmiao Xu; Li Pan, Mounes Aliyari Ghasebeh, Ihab R. Kamel) have conflict of interest.

Ethical approval   All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent   This study was approved by the IRB. Due to the retrospective nature of this study, informed consent was not obtained.

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