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Functional Magnetic Resonance Imaging Response of Targeted Tumor Burden and Its Impact on Survival in Patients With Hepatocellular Carcinoma

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Abstract

Purpose—The aim of this study was to evaluate response of the targeted tumor burden by functional magnetic resonance imaging (MRI) including volumetric diffusion-weighted imaging and volumetric contrast-enhanced MRI (CE-MRI) and its impact on survival in patients with hepatocellular carcinoma treated with intra-arterial therapy (IAT).

Materials and Methods—This institutional review board–approved, Health Insurance Portability and Accountability Act–compliant retrospective study included 157 hepatocellular carcinoma lesions in 97 patients (78 men and 19 women; mean age, 64 years) treated with IAT. All patients had pretreatment and 3- to 4-week follow-up MRI with diffusion-weighted imaging and CE-MRI. All lesions 2 cm or larger that were targeted during the first session of IAT were segmented using research software (MR-Oncotreat) to determine targeted tumor burden relative to liver volume (%). Targeted tumor burden was stratified into low (<10%) or high (>10%). Response using volumetric functional apparent diffusion coefficient (ADC; increase by ≥25%) and CE-MRI (decrease by ≥50% and ≥65% in arterial and venous enhancement [VE], respectively) was assessed in all targeted tumors (range, 1–11) using paired *t* tests. Kaplan-Meier survival analysis was performed and log-rank test was used to compare pairs of survival curves. Multivariate Cox regression analysis was performed to determine the simultaneous effect of treatment response and tumor burden on survival after adjusting for age, sex, and Child Pugh status.

Results—There was a significant increase in volumetric ADC (median, 15%; $P < 0.001$) and a decrease in volumetric arterial enhancement (AE) and VE (median AE, −43% and portal venous phase (PVP), −29%, respectively; $P < 0.001$) 3 to 4 weeks after treatment in the targeted tumor burden. Multivariable Cox regression demonstrated that both ADC response and low tumor burden were independently associated with greater survival (hazard ratios, 0.53 and 0.55; P values, 0.025 and 0.016, respectively) after adjustment for age, sex, and Child Pugh status. Multivariable Cox regression models demonstrated no statistically significant relationship between AE response and survival after adjusting for tumor burden. However, multivariable Cox regression demonstrated that VE response was associated with greater survival only in those with low tumor burden (hazard ratio, 0.10; $P = 0.001$), indicating a strong interaction between VE response and tumor burden.

Conclusion—Quantifying targeted tumor burden is important in predicting patient survival when using functional MRI metrics in assessing treatment response.

Keywords

oncology; functional MRI; liver tumors; treatment response

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is the fifth most common cancer worldwide.^{1,2} It is the third leading cause of cancer-related deaths worldwide and globally accounts for as many as 500,000 deaths annually.¹ Although hepatic resection and transplantation offer a potential for curative therapy, most patients with HCC (70%–80%) are not candidates for curative resection or transplantation because of either advanced stage at the time of initial presentation or because of underlying advanced cirrhosis.^{3,4} Transarterial chemoembolization (TACE) is the most widely used first-line treatment in the Western World and Asia for patients with unresectable HCC. Transarterial chemoembolization is considered the standard of care especially in Barcelona-Clinic Liver Cancer (BCLC) B patients, based on 2 meta-analyses that demonstrated 2-year overall survival benefit.^{5,6} In addition, TACE alone or in combination with laser induced thermotherapy resulted in improved patient survival in patients with unresectable noncolorectal and nonbreast cancer origin.⁷

There is increased interest in determining response of hepatic malignancies to therapy using the entire tumor burden rather than a single index lesion.⁸ In developing RECIST 1.1, the response evaluation criteria in solid tumors (RECIST) working group considered moving from anatomic unidimensional assessment of tumor burden to either volumetric anatomical assessment or to functional assessment. However, this was deemed inappropriate owing to insufficient standardization of the acquisition or image analysis techniques.⁸ Measuring volumetric tumor burden remains critical because patients with extensive hepatic involvement at baseline may have less functioning liver parenchyma and therefore less likelihood for survival after intra-arterial therapy (IAT) compared with those with low tumor burden.⁹ Moreover, in patients with colorectal metastases, the number and size of metastases are significant prognostic factors for long-term survival in patients treated with laser-induced interstitial therapy.¹⁰

Functional imaging techniques are increasingly being used to monitor response to therapy, often predicting the success of therapy before conventional measurements using size change.¹¹⁻¹⁴ The European Association for the Study of the Liver guidelines recommend measuring the enhancing part of the tumor in the axial plane for assessing treatment response; however, enhancement in a single axial plane may not reflect global changes in the entire tumor volume.¹⁵ Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) can quantify tumor vascularity and thus can delineate zones of viable enhancing tumor and zones of tumor necrosis with poor/absent contrast enhancement.¹⁶ Several previous studies reported significant changes in contrast enhancement as well as apparent diffusion coefficient (ADC) after loco-regional therapy.^{13,17,18} Diffusion weighted imaging (DWI) and the generated ADC values can differentiate viable from dead tumor cells by assessing differences in membrane permeability. Successful treatment is reflected by increase in tumor water diffusion values, which manifests as increase in ADC values.¹¹

With advances in image processing techniques, several recent studies have demonstrated changes in both of these functional techniques (ADC and DCE-MRI) in the index tumor volume rather than in a single axial plane.¹⁹⁻²¹ However, to date, there is sparse evidence of the value of assessing response in all targeted tumors using these functional techniques. Therefore, the objective of this study was to evaluate response in the entire targeted tumor burden using functional MRI response and its impact on overall survival in patients with HCC treated by IAT.

MATERIALS AND METHODS

This retrospective study was performed in compliance with the Health Insurance Portability and Accountability Act after we obtained a waiver for informed patient consent from our institutional review board.

Patient Population

A database of patients who underwent IAT with doxorubicin-eluting beads (DEB) TACE for HCC from February 2007 to August 2010 at our institution was reviewed. Inclusion criteria were patients (age ≥ 18 y) diagnosed with HCC who underwent IAT as determined by our liver tumor board and who underwent pretreatment and posttreatment MRI including DWI and contrast-enhanced MRI 3 to 4 weeks after treatment. Exclusion criteria were treatment with concurrent systemic sorafenib (n = 10). Of 97 patients, 58 were treated by conventional TACE and 39 patients were treated by DEB-TACE. Patients were observed until death or until September 2013.

Chemoembolization Technique

All patients underwent 1 session of TACE between baseline MRI and 1-month follow-up MRI. Conventional regimen was based on cisplatin 100 mg, doxorubicin 50 mg, and mitomycin C 10 mg mixed in a 10-mL water-soluble contrast medium.²² For DEB-TACE, beads of 100 to 300 µm in size mixed with a nonionic contrast medium, as described elsewhere, were used.²³

MRI Technique

All 97 patients underwent our standard imaging protocol with pretreatment MRI and 3 to 4 weeks posttreatment MRI. These data served as the source data for all imaging analyses described in this study. A 1.5-T MRI scanner (Siemens MAGNETOM Avanto) using a phased array torso coil was used to perform MRI. The protocol consisted of T2-weighted turbospin-echo images (matrix size, 256×256 ; slice thickness, 8 mm; interslice gap, 2 mm; repetition time [TR]/echo time [TE], 4500/92 milliseconds; received bandwidth, 32 kHz) and breath-hold DWI echoplanar images (matrix, 128×128 ; slice thickness, 8 mm; interslice gap, 2 mm; b value = 0 s/mm², 750 s/mm²; TR, 3000 milliseconds; TE, 69 milliseconds; received bandwidth, 64 kHz). Breath-hold unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadopentetate; Magnevist; Bayer, Wayne, NJ) T1-weighted 3-dimensional fat suppressed spoiled gradient-echo images (field of view, 320-400 mm; matrix, 192×160 ; slice thickness, 2.5 mm; TR, 5.77 milliseconds; TE, 2.77 milliseconds; received bandwidth, 64 kHz; flip angle, 10°) in the arterial (20 seconds), portal venous (70 seconds), and delayed (3 minutes) phase were also obtained.

Magnetic Resonance Image Analysis

A total of 97 patients with 157 treated HCC lesions targeted by IAT were analyzed using proprietary research software, MR Oncotreat, which has been developed in collaboration with Siemens Medical Solutions, USA. DICOM data (T2-weighted images, DWI, ADC maps, T1-weighted images precontrast, arterial and venous phase images) of the baseline and follow-up MRI studies were imported into MR Oncotreat. Image analysis was performed by (V.G.H.) with 4 years of experience in abdominal MRI.

Quantifying Targeted Tumor Volume and Percent Tumor Burden

All lesions 2 cm or larger which were targeted at the first session of IAT were included in this analysis. Targeted tumor borders were defined with an interactive segmentation technique.²⁴ The combined volume of all targeted lesions provided targeted tumor volume. Subsequently, the entire liver was segmented to provide whole liver volume. Targeted tumor burden expressed as percentage was calculated from the formula:

$$\text{Tumor burden (\%)} = \frac{\text{Targeted tumor volume}}{\text{Whole liver volume}} \times 100$$

Quantifying Changes in Volumetric Functional MRI Data After IAT

Volumetric functional data included ADC values, arterial enhancement (AE), and venous enhancement (VE). These were generated at baseline and at follow-up, then compared for percentage change after treatment. The software generates mean ADC of the entire targeted tumor volume. The software also calculates relative AE and VE from the formula

$$\frac{A - U}{A} \times 100 \text{ for AE and } \frac{V - U}{V} \times 100 \text{ for VE, where } A \text{ is enhancement in the arterial phase, } V \text{ is enhancement in the venous phase, and } U \text{ is signal of the unenhanced mass.}$$

Percentage change in volumetric tumor ADC (ADC_{change}) at follow-up compared with

baseline values was calculated using the formula $\frac{ADC_{\text{post}} - ADC_{\text{pre}}}{ADC_{\text{pre}}} \times 100$, where ADC_{pre} is baseline ADC value and ADC_{post} is follow-up ADC value. Tumors were considered responders if the ADC increased by 25% or greater after treatment, as validated in a previous study.²⁵

Percentage change in volumetric tumor enhancement (Enh_{change}) at follow-up compared with baseline values was calculated using the formula

$\frac{\text{Enhancement}_{\text{post}} - \text{Enhancement}_{\text{pre}}}{\text{Enhancement}_{\text{pre}}} \times 100$, where $\text{Enhancement}_{\text{pre}}$ is baseline enhancement and $\text{Enhancement}_{\text{post}}$ is follow-up enhancement. This formula was used for both AE and VE. Tumors were considered responders if AE and VE decreased by 50% or greater and 65% or greater after treatment, respectively, as validated in a previous study.²⁵

Median targeted tumor burden in this cohort was calculated, and patients were considered to have a low burden if their tumor burden was within the median range. Otherwise, patients were stratified into the group with high targeted tumor burden. Overall survival was calculated and compared between the 2 groups. In addition, overall survival for responders and nonresponders by volumetric functional MRI criteria within each group was calculated and compared.

Statistical Analysis

Two-sided paired *t* test was used to compare changes in volumetric functional data before and after IAT. Survival rates were calculated using Kaplan-Meier analysis from the time of first TACE session until September 2013. The log-rank test was used to compare pairs of survival curves. Multivariate Cox regression analysis was performed to determine the simultaneous effect of treatment response and tumor burden on survival after adjusting for age, sex, and Child Pugh status. Pairwise comparisons were performed with SPSS software package (version 16.0), and Cox regression was performed with Stata software package (version 13.1). A *P* value of <0.05 was considered statistically significant.

RESULTS

Demographic Data

Baseline patient demographics and clinical characteristics are summarized in Table 1. Our cohort included 78 men (80%) and 19 women (20%) with a total of 157 HCC lesions. Most were whites (52%) with cirrhosis (77%) and alpha-fetoprotein less than 200 (57%). Of the 97 patients, 58 were treated by conventional TACE and 39 were treated by DEB-TACE. A total of 241 TACE procedures were performed, and average number of procedures was 2.5 per patient. Diagnosis of HCC was confirmed by biopsy in 56 (58%) patients and by imaging alone in 41 (42%) patients.

Overall Survival

Overall survival in patients stratified by BCLC is shown in Figure 1 (Table 2). Median survival for patients with BCLC A, BCLC B, BCLC C, and BCLC D was 52.0, 18.3, 6.8, and 3.7 months, respectively.

Volumetric Targeted Tumor Burden

Median targeted tumor burden was 9.8% of the total liver volume. Patients were stratified into 2 groups: The first included those with low (< 10% of the total liver volume) targeted tumor burden, and the second included those with high (>10% of the total liver volume) targeted tumor burden. Patients with a low targeted tumor burden had improved overall survival compared with patients who had a high tumor burden (median survival, 24.2 vs 10.5 months respectively; $P = 0.016$ by log-rank test) (Fig. 2, Table 3).

Changes in Functional Magnetic Resonance Parameters in Targeted Tumor Burden After IAT

Voxel-wise comparison of volumetric functional MRI data for all targeted lesions before and after treatment showed significant differences (Table 4). Volumetric ADC increased from $1.43 \times 10^{-3} \text{ mm}^2/\text{s}$ to $1.66 \times 10^{-3} \text{ mm}^2/\text{s}$ after initial treatment (median increase, 15%; $P < 0.001$) in all targeted lesions. Volumetric AE decreased from 37% to 23% after treatment (median decrease, -43%; $P < 0.001$) in all treated lesions. Volumetric VE also decreased from 74% to 46% after treatment (median decrease, -29%; $P < 0.0001$) in all targeted lesions.

Impact of Volumetric Tumor Response by Functional MRI Changes on Patient Survival

Changes in volumetric ADC were used to stratify patient survival by responders (> 25% increase in ADC) and nonresponders in those with low (< 10% of total liver volume) and high (>10% of total liver volume) targeted tumor burden (Fig. 3, Table 5). Multivariable Cox regression demonstrated that both ADC response and low tumor burden were independently associated with greater survival (hazard ratios, 0.53 and 0.55, with P values 0.025 and 0.016, respectively) after adjustment for age, sex, and Child Pugh status. Results were similar in a model unadjusted for demographic and clinical covariates.

Changes in volumetric AE were used to stratify patients as responders (> 50% decrease in AE) and nonresponders by tumor burden (Fig. 4, Table 6). Multivariable Cox regression models demonstrated no statistically significant relationship between AE response and survival after adjusting for tumor burden.

Changes in volumetric VE were used to stratify patients as responders (> 65% decrease in VE) and nonresponders in those with low (< 10% of total liver volume) and high (>10% of total liver volume) targeted tumor burden (Fig. 4). Multivariable Cox regression demonstrated that VE response was associated with greater survival only in those with low tumor burden (hazard ratio, 0.10; $P = 0.001$), indicating a strong interaction between VE response and tumor burden.

Finally, a Cox regression model containing both ADC and VE response was constructed. This model demonstrated similar results as the models with ADC and VE responses separately, indicating that these 2 covariates are independent, additive predictors of survival.

DISCUSSION

Quantifying tumor burden is critical in managing patients with HCC who are transplant candidates and is a potential predictor of patient survival.²⁶ Increasing tumor burden reduces the volume of functioning hepatocytes and is often associated with macrovascular invasion and posttransplant recurrence. Preserving hepatic function after IAT is essential because most HCC occurs in background liver cirrhosis with already compromised hepatic function. After IAT, assessing response in all targeted lesions is clinically more valuable compared with assessing response in a single index lesion. This is particularly important in multifocal or diffuse disease, where more than 1 lesion may be targeted. Also, assessing response using volumetric functional MRI metrics has been shown to better stratify responders from nonresponders early (3–4 weeks) after therapy compared with the more delayed response using conventional anatomic metrics.^{25,27}

Value of Quantifying Volumetric Tumor Burden

In our study, perhaps not surprisingly, we noted that patients with a low (<10%) targeted tumor burden had a significant survival advantage compared with patients who had high (>10%) tumor burden (Fig. 2). Tumor size is an important component of the BCLC staging system, and patients with small, noninfiltrating tumors have better survival compared with patients with large, infiltrating tumors. Our data showed that with an increase in BCLC stage, patients had worsening survival (Fig. 1). We hypothesize that this is mainly because of the presence of large tumor volume replacing functioning liver parenchyma, potentially causing vascular invasion and resulting in poor prognosis. With increasing 3-dimensional computed tomography and magnetic resonance acquisitions, it has become possible to generate volumetric tumor measurements efficiently and with high reproducibility.²⁸ The availability of advanced image analysis that can generate accurate tumor volume and total disease burden measurements is definitely advantageous to allow better preprocedure planning especially in case of yttrium 90, where knowledge of tumor volume is used for calculating dose to be delivered to the tumor as well as the background liver.

Changes in Volumetric Functional MRI Early After Therapy

Our study demonstrated significant changes in functional MRI metrics (ADC, AE, VE) after IAT in all 157 targeted lesions (Table 4). As shown in previous studies, these changes occur early (3–4 weeks) after IAT therapy, before changes in anatomic (size) metrics occur.^{12,27,29} This finding is particularly important in the management of patients receiving newer cytostatic rather than cytotoxic agents, where response by conventional size measurements may take several months to document. Confirming early disease stability after IAT is also essential in patients with HCC who are bridged to transplantation. If treatment is repeated unnecessarily, it could result in further deterioration in liver function, which would deem the patient ineligible for surgery. On the other hand, if repeat treatment is delayed because of

lack of anatomic response, new lesions may result in disease progression while the patient is awaiting transplantation.

Assessing Early Response to IAT Using Changes in Volumetric Functional MRI

To our knowledge, this is the first study to use changes in volumetric functional MRI metrics of the entire targeted tumor burden in assessing the response of HCC to IAT. In the current study, patients with change in ADC, AE, or VE above previously documented thresholds were strongly associated with a significant survival benefit compared with all other patients (Figs. 3 and 4). This was particularly noted among patients with low (10%) targeted tumor burden. Based on our data, assessment of response of the targeted tumor burden using these potential MRI biomarkers could help in better stratifying responders and nonresponders (Fig. 5, D and E). These novel functional MRI techniques can predict the success of therapy long before the conventional axial size measurements.²⁹ In addition, changes in ADC alone can be used to assess for tumor response in patients who have contraindications for contrast administration. These results are in agreement with previous studies that demonstrated that early changes by volumetric functional MRI in the index lesion can predict survival in HCC^{12,13,25,27,29,30} and cholangiocarcinoma.²⁰ Similar findings were reported in patients with neuroendocrine liver metastasis.¹⁹

Conventional response criteria were intended for use in patients receiving systemic chemotherapy and include response assessment in more than 1 target or index lesion. Whereas the original RECIST guidelines advocated assessing response in up to 5 lesions per organ, the revised criteria advocated assessing response in fewer (2) lesions. This suggests that the optimum number of lesions that should be used to assess response is uncertain. Previous studies used metabolic tumor burden identified on fluorodeoxyglucose-positron emission tomography for predicting outcomes.^{31,32} These studies were performed on patients with metastatic melanoma and non-small-cell lung cancer. However, HCC is less likely to be fluorodeoxyglucose avid compared with metastatic melanoma and non-small-cell lung cancer. Therefore, these imaging techniques are less likely to be effective in assessing response in patients with HCC.

Multivariable Cox regression models containing ADC response, VE response, and tumor burden demonstrated that all 3 factors are significantly related to patient survival. The relationship involving VE response was significant only in those with low tumor burden. These relationships were not significantly affected after adjustment for age, sex, and Child Pugh status.

This study has limitations. This is a single-institution retrospective study that included patients with HCC who were treated with TACE or DEB-TACE only. This may have included selection bias. However, we opted to include only these patients to reduce potential heterogeneity of response in patients who were treated with other IATs such as theraspheres. Pathologic confirmation of tumor necrosis remains the gold standard for assessing response to treatment. However, this is available only in select cases that undergo resection or transplantation. In addition, biopsy is not without complications and is often not clinically indicated. Another limitation of this study is that arterial phase images were acquired using a 20-second fixed delay. This could potentially limit the value of arterial phase images in

assessing treatment response. However, reduction in both arterial and portal venous phase enhancement after therapy was statistically significant ($P < 0.001$). It is unlikely that using a timing bolus would impact the value of quantifying disease burden. In this study, we used overall survival as our primary endpoint because this is what is commonly used in clinical trials. We believe that this is a better outcome than assessment of tumor necrosis pathologically.

In summary, patients with change in ADC, AE, or VE above previously documented thresholds were strongly associated with a significant survival benefit compared with all other patients, particularly among patients with low (< 10%) targeted tumor burden. Based on our data, assessment of response of the targeted tumor burden using these potential MRI biomarkers could help in better stratifying responders and nonresponders. Further validation in large clinical trials is suggested.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001; 94:153–156. [PubMed: 11668491]
2. Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology*. 2002; 122:1609–1619. [PubMed: 12016426]
3. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology*. 2002; 35:519–524. [PubMed: 11870363]
4. Yuen MF, Cheng CC, Laufer JJ, et al. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. *Hepatology*. 2000; 31:330–335. [PubMed: 10655254]
5. Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002; 224:47–54. [PubMed: 12091661]
6. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003; 37:429–442. [PubMed: 12540794]
7. Vogl TJ, Kreutztrager M, Gruber-Rouh T, et al. Neoadjuvant TACE before laser induced thermotherapy (LITT) in the treatment of non-colorectal non-breast cancer liver metastases: feasibility and survival rates. *Eur J Radiol*. 2014; 83:1804–1810. [PubMed: 25082479]
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45:228–247. [PubMed: 19097774]
9. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002; 359:1734–1739. [PubMed: 12049862]
10. Vogl TJ, Dommernuth A, Heinle B, et al. Colorectal cancer liver metastases: long-term survival and progression-free survival after thermal ablation using magnetic resonance-guided laser-induced interstitial thermotherapy in 594 patients: analysis of prognostic factors. *Invest Radiol*. 2014; 49:48–56. [PubMed: 24056114]
11. Padhani AR, Khan AA. Diffusion-weighted (DW) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) for monitoring anticancer therapy. *Target Oncol*. 2010; 5:39–52. [PubMed: 20383784]
12. Kamel IR, Bluemke DA, Eng J, et al. The role of functional MR imaging in the assessment of tumor response after chemoembolization in patients with hepatocellular carcinoma. *J Vasc Interv Radiol*. 2006; 17:505–512. [PubMed: 16567675]
13. Kamel IR, Liapi E, Reyes DK, et al. Unresectable hepatocellular carcinoma: serial early vascular and cellular changes after transarterial chemoembolization as detected with MR imaging. *Radiology*. 2009; 250:466–473. [PubMed: 19188315]

14. Kamel IR, Reyes DK, Liapi E, et al. Functional MR imaging assessment of tumor response after 90Y microsphere treatment in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol.* 2007; 18(1 pt 1):49–56. [PubMed: 17296704]
15. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma: conclusions of the Barcelona-2000 EASL conference: European Association for the Study of the Liver. *J Hepatol.* 2001; 35:421–430. [PubMed: 11592607]
16. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases: management of hepatocellular carcinoma. *Hepatology.* 2005; 42:1208–1236. [PubMed: 16250051]
17. Kalb B, Chamsuddin A, Nazzal L, et al. Chemoembolization follow-up of hepatocellular carcinoma with MR imaging: usefulness of evaluating enhancement features on one-month posttherapy MR imaging for predicting residual disease. *J Vasc Interv Radiol.* 2010; 21:1396–1404. [PubMed: 20688534]
18. Rhee TK, Naik NK, Deng J, et al. Tumor response after yttrium-90 radioembolization for hepatocellular carcinoma: comparison of diffusion-weighted functional MR imaging with anatomic MR imaging. *J Vasc Interv Radiol.* 2008; 19:1180–1186. [PubMed: 18656011]
19. Gowdra Halappa V, Corona-Villalobos CP, Bonekamp S, et al. Neuroendocrine liver metastasis treated by using intraarterial therapy: volumetric functional imaging biomarkers of early tumor response and survival. *Radiology.* 2013; 266:502–513. [PubMed: 23192780]
20. Halappa VG, Bonekamp S, Corona-Villalobos CP, et al. Intrahepatic cholangiocarcinoma treated with local-regional therapy: quantitative volumetric apparent diffusion coefficient maps for assessment of tumor response. *Radiology.* 2012; 264:285–294. [PubMed: 22627601]
21. Li Z, Bonekamp S, Halappa VG, et al. Islet cell liver metastases: assessment of volumetric early response with functional MR imaging after transarterial chemoembolization. *Radiology.* 2012; 264:97–109. [PubMed: 22627602]
22. Geschwind JF, Ramsey DE, Cleffken B, et al. Transcatheter arterial chemoembolization of liver tumors: effects of embolization protocol on injectable volume of chemotherapy and subsequent arterial patency. *Cardiovasc Intervent Radiol.* 2003; 26:111–117. [PubMed: 12616414]
23. Lencioni R, de Baere T, Burrel M, et al. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. *Cardiovasc Intervent Radiol.* 2012; 35:980–985. [PubMed: 22009576]
24. Grady L. Random walks for image segmentation. *IEEE Trans Pattern Anal Mach Intell.* 2006; 28:1768–1783. [PubMed: 17063682]
25. Bonekamp S, Li Z, Geschwind JF, et al. Unresectable hepatocellular carcinoma: MR imaging after intraarterial therapy, part I: Identification and validation of volumetric functional response criteria. *Radiology.* 2013; 268:420–430. [PubMed: 23616631]
26. Toso C, Trotter J, Wei A, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl.* 2008; 14:1107–1115. [PubMed: 18668667]
27. Bonekamp S, Halappa VG, Geschwind JF, et al. Unresectable hepatocellular carcinoma: MR imaging after intraarterial therapy. Part II. Response stratification using volumetric functional criteria after intraarterial therapy. *Radiology.* 2013; 268:431–439. [PubMed: 23616632]
28. Lin M, Pellerin O, Bhagat N, et al. Quantitative and volumetric European Association for the Study of the Liver and Response Evaluation Criteria in Solid Tumors measurements: feasibility of a semiautomated software method to assess tumor response after transcatheter arterial chemoembolization. *J Vasc Interv Radiol.* 2012; 23:1629–1637. [PubMed: 23177109]
29. Bonekamp S, Jolepalem P, Lazo M, et al. Hepatocellular carcinoma: response to TACE assessed with semiautomated volumetric and functional analysis of diffusion-weighted and contrast-enhanced MR imaging data. *Radiology.* 2011; 260:752–761. [PubMed: 21771960]
30. Corona-Villalobos CP, Zhang Y, Zhang WD, et al. Magnetic resonance imaging of the liver after loco-regional and systemic therapy. *Magn Reson Imaging Clin N Am.* 2014; 22:353–372. [PubMed: 25086934]

31. Fonti R, Larobina M, Del Vecchio S, et al. Metabolic tumor volume assessed by 18F-FDG PET/CT for the prediction of outcome in patients with multiple myeloma. *J Nucl Med.* 2012; 53:1829–1835. [PubMed: 23071351]
32. Zhang H, Wroblewski K, Liao S, et al. Prognostic value of metabolic tumor burden from (18)F-FDG PET in surgical patients with non-small-cell lung cancer. *Acad Radiol.* 2013; 20:32–40. [PubMed: 22999369]

FIGURE 1.

Survival in months stratified by BCLC. Figure 1 can be viewed online in color at www.investigativeradiology.com.

FIGURE 2.

Pretreatment survivals in months stratified by targeted tumor burden (TB). Figure 2 can be viewed online in color at www.investigativeradiology.com.

FIGURE 3.

Survival stratified by ADC response (25% increase) in patients with low (10%) and high (>10%) targeted tumor burden (TB). Figure 3 can be viewed online in color at www.investigativeradiology.com.

FIGURE 4.

Survival in months stratified by (A) arterial (50% decrease) and (B) portal venous (65% decrease) phase response in patients with low (10%) and high (>10%) targeted tumor 7.

Figure 4 can be viewed online in color at www.investigativeradiology.com.

FIGURE 5.

Tumor burden of hepatocellular carcinoma at baseline and after treatment. Hepatocellular carcinoma with a high tumor burden (A) before treatment lesions. (B) 3D segmented tumors. (C) Segmented whole liver.

Tumor burden = $\frac{\text{Tumor volume in } B}{\text{Whole liver volume in } C} \times 100 = \frac{431.3}{1413.1} \times 100 = 30.5\%$. D, Volumetric ADC map demonstrating increase in volumetric ADC from $1.26 \times 10^{-3} \text{ mm}^2/\text{sec}$ to $1.91 \times 10^{-3} \text{ mm}^2/\text{sec}$ (51.6% increase) early after treatment as depicted in the histogram (blue, pretreatment; orange, posttreatment). There is a rightward shift in the blended histogram representing an increase in ADC after treatment and favorable response to therapy. E, Volumetric enhancement characteristics in the same patient described in Figure 4. Volumetric enhancement map in PVP. Enhancement in PVP decreased from 75.4% to 35.9% (52.3% decrease) early after treatment as depicted in the histogram (blue, pretreatment; orange, posttreatment). There is a leftward shift in the blended histogram representing a decrease in enhancement after treatment and favorable response to therapy. Figure 5 can be viewed online in color at www.investigativeradiology.com.

TABLE 1Demographics and Clinical Characteristics in Our Patient Population (n = 97)¹⁶

	n	%
Age, mean $\pm$ SD, y	63 $\pm$ 12	
Race/Ethnicity		
White	50	52
African American	34	35
Others	13	13
Sex		
Male	78	80
Female	19	20
Etiology		
Hepatitis C	28	30
Hepatitis B	15	15
ALD	7	7
Hep B and Hep C	1	1
HIV and Hep C	4	4
NASH	2	2
Cryptogenic cirrhosis	2	2
Alagille syndrome	1	1
HIV and Hep B	1	1
HIV Hep C, and ALD	1	1
HIV, Hep B, and Hep C	3	3
Hep B, Hep C, and ALD	1	1
Unknown	31	32
AFP		
200	42	43
<200	55	57
Imaging		
Cirrhosis	75	77
Present	22	23
Absent		
Tumor distribution		
Solitary	43	44
Multifocal	42	43
Infiltrative	12	13
Child-Pugh class		
A	55	57
B	35	36
C	7	7
BCLC stage		
A	19	20

	n	%
B	36	37
C	34	35
D	8	8
Okuda stage		
1	35	36
2	49	51
3	13	13

AFP indicates alfa-fetoprotein; ALD, alcoholic liver disease; BCLC, Barcelona-Clinic Liver Cancer; Hep, hepatitis; HIV, human immunodeficiency virus; NASH, nonalcoholic steatohepatitis.

TABLE 2

Survival in Months Stratified by BCLC

BCLC	Mean Survival in Months (95% CI)	Median Survival in Months (95% CI)
BCLC A	48.2 (37.4–59.0)	52.0 (–)
BCLC B	34.7 (26.5–43.8)	18.3 (0–36.6)
BCLC C	11.8 (7.4–16.1)	6.8 (3.5–10.1)
BCLC D	14.8 (1.4–28.2)	3.7 (0.5–7.0)

BCLC indicates Barcelona Clinic Liver Cancer; CI, confidence interval.

TABLE 3

Pretreatment Survival in Months Stratified by Targeted Tumor Burden

Tumor Burden	Mean Survival in Months (95% CI)	Median Survival in Months (95% CI)
Low (≤ 10%)	33.8 (26.2–41.3)	24.2 (13.3–35.1)
High (>10%)	21.8 (14.7–28.9)	10.5 (8.5–12.5)

CI indicates confidence interval.

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TABLE 4

Paired *t* Tests for Comparison of MR Imaging Variables in Our Cohort of 97 Patients With Treated Hepatocellular Carcinoma (Total of 157 Lesions)

Functional Parameters in Targeted Tumor Burden	Before Treatment	3–4 Weeks After Treatment	Median % Change	<i>P</i>
Volumetric ADC, $\times 10^{-3} \text{ mm}^2/\text{s}$	1.43 ± 0.33	1.66 ± 0.40	15	<0.001
Volumetric AE, %	37 ± 26	23 ± 22	–43	<0.001
Volumetric VE, %	74 ± 31	46 ± 31	–29	<0.001

ADC indicates apparent diffusion coefficient; AE, arterial enhancement; MR, magnetic resonance; VE, venous enhancement.

TABLE 5Survival in Months Stratified by ADC Response ($\geq 25\%$ Increase) and Targeted Tumor Burden

Response by ADC and Tumor Burden	Mean Survival in Months (95% CI)	Median Survival in Months (95% CI)
Responders in tumor burden $\leq 10\%$	41.6 (29.9–53.3)	45.2 (14.7–75.6)
Non responders in tumor burden $\leq 10\%$	28.6 (19.4–37.8)	16.8 (2.6–30.9)
Responders in tumor burden $>10\%$	30.9 (14.6–47.2)	11.4 (0–25.1)
Non responders in tumor burden $>10\%$	18.4 (11.2–25.6)	9.5 (6.7–12.3)

ADC indicates apparent diffusion coefficient; CI, confidence interval.

TABLE 6

Survival in Months Stratified by AE and TB and by PVP and TB

	Mean Survival in Months (95% CI)	Mean Survival in Months (95% CI)
Response by AE and TB		
Responders in TB 10% (1)	40.1 (28.2–52.1)	45.2 (*)
Nonresponders in TB 10% (2)	27.2 (18.9–35.5)	18.8 (8.2–29.3)
Responders in TB >10% (3)	19.5 (11.1–28.0)	11.4 (8.8–14.0)
Nonresponders in TB >10% (4)	23.6 (13.0–34.1)	8.8 (1.3–16.2)
Response by PVP and TB		
Responders in TB 10% (5)	61.1 (52.0–70.2)	*
Nonresponders in TB 10% (6)	18.4 (12.9–23.8)	11.8 (7.0–16.5)
Responders in TB >10% (7)	19.6 (10.0–29.2)	11.4 (8.9–13.9)
Nonresponders in TB >10% (8)	21.8 (13.6–30.0)	9.5 (6.4–12.6)

Numbers in parenthesis described survival in Kaplan-Meier curve (Fig. 4).

AE indicates arterial enhancement; TB, tumor burden; PVP, portal venous phase; CI, confidence interval.

* Median survival could not be calculated because of decreased number of events.