Published in final edited form as:

J Comput Assist Tomogr. 2011 ; 35(2): 167–173. doi:10.1097/RCT.0b013e3182004bfb.

Early Response of Hepatic Malignancies to Locoregional Therapy—Value of Diffusion-Weighted Magnetic Resonance Imaging and Proton Magnetic Resonance Spectroscopy

Susanne Bonekamp, DVM, PhD*, Jialin Shen, MD†, Nouha Salibi, PhD‡, Hong C. Lai, PhD*, Jeff Geschwind, MD*, and Ihab R. Kamel, MD*

*Russell H Morgan Department of Radiology and Radiology Science, Johns Hopkins University School of Medicine, Baltimore, MD

†Department of Radiology, Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

‡Siemens Corporate Research, Princeton, NJ

Abstract

Purpose—The objective of our study was to determine the usefulness of the diffusion-weighted magnetic resonance imaging and proton magnetic resonance spectroscopy (¹H-MRS) of hepatic malignancies for the assessment of response to locoregional treatment.

Methods—Forty-four patients (29 men; mean age, 58 years) with hepatic malignancies were treated locally. Magnetic resonance imaging examinations obtained before and at 1 and 6 months after transarterial chemoembolization were analyzed retrospectively. Imaging criteria included change in tumor size, percentage of enhancement in the arterial and portal venous phases, diffusion-weighted magnetic resonance imaging apparent diffusion coefficients, and choline concentration by quantitative ¹H-MRS. Response to treatment was grouped according to RECIST (Response Evaluation Criteria in Solid Tumors) and European Association for the Study of the Liver (EASL) criteria based on magnetic resonance imaging at 6 months after treatment. Statistical analysis used paired t test, Fisher exact test, and univariate and multivariate Cox proportional hazards models.

Results—Before treatment, the median tumor diameter was 6 cm; at 6 months after treatment, median tumor diameter was 5.1 cm. According to RECIST and EASL, 66% of the patients achieved partial response, 31% had stable disease, and 3% of the patients showed progressive disease. One month after transarterial chemoembolization, apparent diffusion coefficient increased ($P < 0.14$), and mean choline concentration of the tumors decreased ($P < 0.008$).

Conclusions—Diffusion-weighted imaging and hepatic choline levels by ¹H-MRS could predict response to locoregional therapy.

Keywords

magnetic resonance imaging; magnetic resonance spectroscopy; diffusion-weighted imaging; liver cancer

Liver cancer is the sixth most common cancer worldwide in terms of numbers of cases, but because of the very poor prognosis, it is the third most common cause of death from cancer.¹

Treatment with systemic chemotherapy and radiation therapy is relatively ineffective. To date, the only potentially curative measure is surgical resection.^{2,3}

However, most hepatocellular carcinoma (HCC) patients (approximately 75%) are not candidates for curative treatments either because of poor liver function or the presence of advanced disease. Furthermore, tumor progression may prevent some patients from undergoing transplantation.⁴ A wait of more than 6 months has been shown to be associated with a dropout rate of 23% to 40% from the waiting list.^{5,6}

Locoregional therapy, including cryoablation, percutaneous ethanol ablation, microwave ablation, radiofrequency ablation, transarterial chemoembolization (TACE), radiotherapy, and yttrium-90 microspheres, has been shown to improve survival among patients with unresectable hepatic neoplasms.⁷

Evaluation of response to treatment is a key aspect in cancer therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) criteria are used in most oncology trials.^{8,9} However, the RECIST criteria evaluate only unidimensional tumor measurements and disregard the extent of necrosis, which is the target of all effective locoregional therapies. The European Association for the Study of the Liver (EASL) guidelines recommended that assessment of tumor response should incorporate the reduction in viable tumor burden, which is commonly assessed using contrast-enhanced imaging.⁴ A number of months are usually required to confirm a change in the tumor size. This means that, in the worst case, there would be little time left to retreat the lesion or switch to another treatment regimen in the event that the initial treatment proved ineffective. If treatment efficacy could be predicted early after starting locoregional therapy, it would be possible to design an appropriate treatment regimen for patients with unresectable hepatic neoplasm. This capability would permit the opportunity to tailor chemotherapy to each patient's response.

Diffusion-weighted magnetic resonance imaging (DWI) and proton magnetic resonance spectroscopy (¹H-MRS) have been suggested to be robust and reproducible early biomarkers of response to anticancer therapy. DWI depends on the microscopic mobility of water (protons). This mobility, classically called brownian motion, is due to thermal agitation and in vivo is impeded by cellular packing, intracellular elements, membranes, and macromolecules. Most studies of DWI use the apparent diffusion coefficient (ADC) as a measure of diffusion. ADC maps are calculated by measuring at least 2 image sets with different *b* values: one with a low *b* value (*b* ≈ 0) and one with a high *b* value (typically 500 > *b* > 1000 s/mm²). Areas with high diffusion will have a high ADC value and appear consequently hyperintense on the ADC maps. Areas with restricted diffusion will appear

hypointense on the ADC maps. ADC values for distinguishing malignancy from benign disease are dependent on histological characteristics such as tumor type, differentiation, and necrosis.¹⁰ Prior studies found that successful treatment was reflected by an increase in ADC values, suggesting increasing cellular necrosis.^{11–18} However, transient early decreases in ADC values can be seen after treatment. Unsuccessful treatment results in remaining or recurring areas of low ADC.^{11–17,19}

Proton magnetic resonance spectroscopy provides a noninvasive method of studying metabolism in vivo. Single-voxel ¹H-MRS has been successfully utilized as a diagnostic tool for tumors in the brain, breast, and prostate and for the evaluation of treatment response to chemotherapy in tumors of the head and neck.^{20–25} The diagnostic value of ¹H-MRS is typically based on the detection of elevated levels of choline compounds (CHO), which are a marker of active tumors. The CHO peak (resonance at 3.2 ppm) includes choline, phosphocholine, glycerophosphocholine, and taurine. Choline is an indicator of cell density and cell wall turnover. Elevated CHO levels are found in tumors. In malignant lesions, the signals from CHO increase significantly. In patients with HCC reexamined shortly after TACE, reduced CHO and reduced CHO/lipid ratios were observed.^{18,26,27}

The purpose of the current study was to determine the usefulness of ADC values and CHO concentration for assessing the early response of unresectable hepatic malignancies to TACE.

MATERIALS AND METHODS

Patients

For this retrospective Health Insurance Portability and Accountability Act–compliant study, we reviewed the imaging and clinical records of 56 patients who underwent DWI and MRS as part of their clinical MRI between June 2006 and May 2008. Institutional review board permission was obtained for retrospective assessment of imaging and clinical data, along with a waiver of informed consent. Patients were excluded if the DW images contained artifacts that precluded ADC measurements ($n = 3$) or the ¹H-MRS voxel was placed outside the lesion ($n = 9$). The remaining 44 patients were included in this study.

MR Technique

Studies were performed on a clinical 1.5-T whole-body system (1.5-T MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with the standard ¹H-MRS acquisition and processing software provided by the manufacturer. Magnetic resonance data were acquired before TACE, 1 to 2 months after TACE, and 6 months after TACE. The imaging protocol included (1) axial T2-weighted fast spin-echo imaging; (2) axial single-shot breath-hold spin-echo echo-planar DW echo-planar imaging (20-second breath-hold periods; field of view, 380 mm; slice thickness, 8 mm; b value 1 = 0 s/mm²; b value 2 = 750 s/mm²; repetition time [TR] = 3000 milliseconds; echo time [TE] = 69 milliseconds); (3) ¹H-MRS with and without water suppression (point resolved single voxel spectroscopy, TR = 1500 milliseconds, TE = 135 milliseconds, 10 averages, 15-second breath-hold periods, automated 3-dimensional [3D] shim); and (4) axial breath-hold unenhanced and contrast-

enhanced T1-weighted 3D fat-suppressed spoiled gradient-echo (generalized autocalibrating partial parallel acquisition, 20- to 26-second breath-hold periods; field of view, 400 mm; slice thickness, 2.5 mm, TR = 5.77 milliseconds, TE = 2.77 milliseconds) in the arterial, portal venous, and delayed phases (20, 60, and 180 seconds, respectively). The spectroscopic voxel was positioned within the liver tumor based on a combination of 3D gradient-echo T1 images and T2 sagittal images, to cover the entire lesion with minimal inclusion of surrounding tissue.

DWI Analysis

ADC values were measured by placing a region of interest over the entire area of the treated mass, avoiding artifact regions. Region-of-interest placement was confirmed through coregistered contrast-enhanced images. Additional regions of interest of the healthy liver parenchyma and spleen were acquired for quality control purposes. The final ADC value in each case was determined by means of the average of all sections obtained.

MR Spectroscopic Evaluation

The ^1H -MR spectra of the tumor and healthy liver parenchyma were analyzed using the Siemens spectroscopy software package by a spectroscopy expert (N.S.). The raw data were zero-filled once (from 1024 to 2048 points), apodized with a Gaussian filter, Fourier transformed, and phase and baseline corrected. Choline peak area and line-width were measured, and CHO concentration was calculated with the internal tissue water reference technique using the following equation:

$$[\text{Cho}] = \frac{I_{\text{Cho}}}{I_{\text{water}}} \times \frac{n_{\text{water}}}{n_{\text{Cho}} \times MW_{\text{water}}} \times \frac{f T1_{\text{water}}}{f T1_{\text{Cho}}} \times \frac{f T2_{\text{water}}}{f T2_{\text{Cho}}}$$

where [Cho] is the concentration of choline in the tumor; I_{Cho} is the integral value of choline at 3.22 ppm; I_{water} is the integral value of the unsuppressed water signal; n_{Cho} and n_{water} are the numbers of ^1H nuclei contributing to the choline and water resonances, respectively; $n_{\text{Cho}} = 9$ for the three CH_3 groups of Cho contributing to the signal at 3.22 ppm; and $n_{\text{water}} = 2$ for the 2 water protons. MW_{water} is the molecular weight of water; $fT1$, or $[1 - \exp(-\text{TR} / T1)]$, is the T1 correction factor for partial saturation; $fT2$, or $[\exp(-\text{TE} / T2)]$, is the correction factor for signal loss from T2 relaxation. Relaxation times T1 and T2 of choline and water in tumor voxels of individual patients were not available for this retrospective analysis of already existing data. The relaxation times used here were measured at 1.5 T in liver tumors of 2 rabbits. T1 was measured using TE of 30 milliseconds and 8 values of TR between 500 and 6000 milliseconds. T2 was measured using TR of 2000 milliseconds and 8 TE values between 30 and 400 milliseconds. The resulting relaxation times are $T1_{\text{cho}}$ of (1293 ± 75) milliseconds, $T1_{\text{water}}$ of (912 ± 200) milliseconds, $T2_{\text{cho}}$ of (276 ± 30) milliseconds, and $T2_{\text{water}}$ of (86 ± 9) milliseconds.

Response to Treatment

Using precontrast and postcontrast MRI data acquired 6 months after treatment, response to treatment was evaluated using RECIST⁹ and EASL^{4,28} criteria and grouped into responders and nonresponders as shown in Table 1.

Statistical Analysis

Paired Student *t* test and Fisher exact test were used to determine if differences between responders and nonresponders were significant. Univariate and multivariate Cox proportional hazards models were applied to determine the likelihood of response to treatment based on changes in choline content by ¹H-MRS and diffusion by DWI. For all analyses, 2-sided statistical tests were used. *P* ≤ 0.05 or less was considered statistically significant. SAS version 9.2 (SAS Institute Inc, Cary, NC) was used for all statistical analyses.

RESULTS

Demographic Data

Forty-four patients with hepatic malignancies were included. The median age was 59 years (interquartile range [IQR], 48–70 years); 29 (66%) patients were male; 7 (16%) patients were of African American descent, 4 (9%) Asian, 1 (2%) Hispanic, and 32 (73%) were white. Twenty-nine patients (66%) had primary liver cancer (HCC), 4 (9%) neuroendocrine metastasis, 4 (9%) colorectal cancer metastasis, 4 (9%) cholangiocarcinoma, and 3 (7%) had other metastatic cancer lesions. The median time between pretreatment MRI and TACE was 15 days (IQR, 2–29.5 days). The median time between treatment and first MR follow-up was 26 days (IQR, 22–60 days). The tumor characteristics before TACE are shown in Table 2.

Tumor Response

One to 2 months after treatment, the median (IQR) tumor size was 6 cm (4.28–9.2 cm) in axial diameter, and the median (IQR) largest axial area was 30.29 cm² (15.13–65.51 cm²). Tables 3 and 4 summarize the early changes after treatment (1–2 months) in ADC values and choline content grouped by RECIST and EASL criteria assessed at 6 months, respectively. Six months after treatment, most hepatic malignancies (66%) showed decrease in size and enhancement, indicating treatment response. The median (IQR) values for largest diameter and largest axial area were 5.1 cm (3.85–8.83 cm) and 22.66 cm² (12.91–53.29 cm²), respectively.

Early Changes in ADC

Early response to treatment at 1 to 2 months included an increase in mean ADC overall (Figs. 1 and 2). Seventy-six percent (21/28) of patients with increased tumor ADC at 1 to 2 months after TACE treatment showed response to the treatment according to EASL or RECIST (Fig. 1B). Forty-seven percent (7/15) of patients with stable or decreased tumor ADC at 1 to 2 months after TACE showed response to the treatment (Fisher exact test, 2-sided *P* = 0.092). Univariate Cox proportional hazards model suggested that those whose

tumor ADC measures increased after the initial treatment were 3.5 times more likely to show response to the treatment (relative risk [RR], 3.5; 95% confidence interval [CI], 1.2–10.5; $P = 0.027$) according to EASL or RECIST. Multivariate Cox proportional hazards model showed an increase in tumor ADC after initial treatment was independently associated with a shorter time to respond to therapy (RR, 4.4; 95% CI, 1.4–14.1).

Early Changes in ^1H -MRS

After treatment, mean choline content of the tumors decreased overall (Figs. 3, 4 and 5). Of patients whose tumor showed decreased choline levels after treatment, 82.8% (24/29) showed response according to EASL or RECIST (Fig. 3B), compared with 33.3% (5/15) of patients with stable or increased tumor choline levels (Fisher exact test, 2-sided $P = 0.002$). Univariate Cox proportional hazards model suggested that those patients whose choline levels decreased after the initial treatment were 4 times more likely to respond to the treatment (RR, 4.0; 95% CI, 1.2–13.3; $P = 0.027$). Multivariate Cox proportional hazards model showed a decrease in choline levels after initial treatment was independently associated with a shorter time to respond to therapy (RR, 3.8; 95% CI, 1.1–13.3).

DISCUSSION

Assessment of the response of hepatic malignancies to locoregional therapy is crucial for determining the need for repeated local treatment or alternative treatment approaches. Furthermore, an objective response may become a surrogate marker of improved survival. Most traditional criteria involve change in lesion size or reduction in enhanced areas using dynamic imaging techniques (EASL, RECIST).^{4,9,28} These can be difficult to evaluate owing to the presence of changes in signal intensity related to injection of iodized oil or hemorrhagic necrosis. Furthermore, cellular death and vascular changes in response to treatment can both precede changes in lesion size, and changes in DWI have the potential to prospectively predict the success of vascular disruptive treatments and for therapies that induce apoptosis.¹⁰ Diffusion-weighted magnetic resonance imaging is quick (single breath-hold), and ADC thresholds can be established and used for diagnosis of complete tumor necrosis. In a recent study, Mannelli et al²⁹ found that viable tumor had restricted diffusion compared with necrotic portions of HCC after TACE, confirming previous findings.^{11,12} The ADC of necrotic tumor tissue was significantly higher than that of viable tumor tissue ($P < 0.0001$).²⁹ Although our study lacked histopathologic correlation, we found that an increase in ADC values early after TACE could predict reduction in tumors size later on. Tumor size, on the other hand, was not changed at 4 weeks after TACE. However, 66% of the lesions showed tumor size reduction at 6 months, again supporting our assumption that DWI can provide an early marker of tumor response, whereas RECIST cannot assess the tumor response to TACE at this early stage. Furthermore, it is possible that some lesions with increased ADC would have shown a decrease in size at a later stage or that histopathologic confirmation of necrosis could have been made in those cases.

The usefulness of ^1H -MRS in evaluating responses to treatment has been reported for various malignancies including HCC.^{18,25,30} Quantification of the choline concentration is essential to characterize changes after TACE. Several quantification techniques have been

used for in vivo ^1H -MRS.^{24,31,32} Quantification is the procedure to estimate numerical values of metabolite concentrations by comparing in vivo signals from a volume of interest to a standard signal from an internal or external reference. Several studies performed ^1H -MRS using an external reference. Unfortunately, this procedure, which requires accurate calibration, is extensive and therefore impractical in the clinical setting. For this reason, water was used as an internal reference in this study.^{33,34} In our in vivo ^1H -MR spectroscopy study, we found a decrease in choline content early after TACE was followed by a decrease in size at a later stage, and more decrease in choline content was seen in lesions that could be categorized as partial response according to RECIST or EASL compared with lesions that were categorized as stable or progressive disease. Again, the lack of correlation between choline content and size or RECIST and EASL criteria in a small number of cases could possibly have been resolved by histopathologic confirmation of cell death or follow-up MRI at a later time point. However, neither was available within this study.

Overall, our study had several limitations. First, we investigated a diverse patient population, and the response to TACE may differ between primary and secondary hepatic malignancies. Second, we studied a small patient population in a retrospective fashion. Third, we had no pathological correlations of the hepatic lesions. Fourth, we used a single, relatively large box-shaped voxel in our MRS study, and we were not able to retrospectively measure relaxation times for individual liver tumors. Contamination error and partial volume effect as well as possible variations in relaxation times may have influenced the obtained values. Finally, we did not investigate the significance of the lipid peaks in the MR spectra, which have been suggested as a more accurate marker of necrosis. Furthermore, image distortions and susceptibility artifacts were unavoidable to some degree and made a definite differentiation between necrotic parts and viable parts of the tumor after treatment difficult.

In this study, the ability of 2 noninvasive MR techniques (^1H -MRS and DWI) to assess early response to TACE of hepatic malignancies was evaluated. The RECIST and EASL criteria at 6 months were used to categorize lesions into partial response, stable disease, and progressive disease categories. The study demonstrated that both ^1H -MRS and DWI early after treatment are good predictors of response to the treatment at 6 months (RR, 4.0; 95% CI, 1.2–13.3; $P = 0.027$; and RR, 3.5; 95% CI, 1.2–10.5; $P = 0.026$, respectively). A combination of ^1H -MRS (for choline), DWI (for ADC), and contrast-enhanced MRI may be optimal for assessing the early therapeutic responses after TACE and for guiding patient care and should be investigated in a larger patient population.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005; 55:74–108. [PubMed: 15761078]
2. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol.* 2009; 10:35–43. [PubMed: 19058754]
3. Varona MA, Del Pino JM, Barrera M, et al. Hepatocellular carcinoma and liver transplantation: a 12-year experience. *Transplant Proc.* 2009; 41:1005–1008. [PubMed: 19376411]

4. 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]
5. Maluf D, Fisher RA, Maroney T, et al. Non-resective ablation and liver transplantation in patients with cirrhosis and hepatocellular carcinoma (HCC): safety and efficacy. *Am J Transplant.* 2003; 3:312–317. [PubMed: 12614287]
6. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology.* 1999; 30:1434–1440. [PubMed: 10573522]
7. Marrero JA, Welling T. Modern diagnosis and management of hepatocellular carcinoma. *Clin Liver Dis.* 2009; 13:233–247. [PubMed: 19442916]
8. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer.* 2006; 42:1031–1039. [PubMed: 16616487]
9. 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]
10. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia.* 2009; 11:102–125. [PubMed: 19186405]
11. 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]
12. Kamel IR, Bluemke DA, Ramsey D, et al. Role of diffusion-weighted imaging in estimating tumor necrosis after chemoembolization of hepatocellular carcinoma. *AJR Am J Roentgenol.* 2003; 181:708–710. [PubMed: 12933464]
13. Liapi E, Geschwind JF, Vossen JA, et al. Functional MRI evaluation of tumor response in patients with neuroendocrine hepatic metastasis treated with transcatheter arterial chemoembolization. *AJR Am J Roentgenol.* 2008; 190:67–73. [PubMed: 18094295]
14. Vossen JA, Buijs M, Liapi E, et al. Receiver operating characteristic analysis of diffusion-weighted magnetic resonance imaging in differentiating hepatic hemangioma from other hypervascular liver lesions. *J Comput Assist Tomogr.* 2008; 32:750–756. [PubMed: 18830105]
15. Vossen JA, Kamel IR, Buijs M, et al. Role of functional magnetic resonance imaging in assessing metastatic leiomyosarcoma response to chemoembolization. *J Comput Assist Tomogr.* 2008; 32:347–352. [PubMed: 18520535]
16. Deng J, Miller FH, Rhee TK, et al. Diffusion-weighted MR imaging for determination of hepatocellular carcinoma response to yttrium-90 radioembolization. *J Vasc Interv Radiol.* 2006; 17:1195–1200. [PubMed: 16868174]
17. Yuan Z, Ye XD, Dong S, et al. Role of magnetic resonance diffusion-weighted imaging in evaluating response after chemoembolization of hepatocellular carcinoma. *Eur J Radiol.* 2009
18. Chen CY, Li CW, Kuo YT, et al. Early response of hepatocellular carcinoma to transcatheter arterial chemoembolization: choline levels and MR diffusion constants—initial experience. *Radiology.* 2006; 239:448–456. [PubMed: 16569781]
19. Marugami N, Tanaka T, Kitano S, et al. Early detection of therapeutic response to hepatic arterial infusion chemotherapy of liver metastases from colorectal cancer using diffusion-weighted MR imaging. *Cardiovasc Intervent Radiol.* 2009; 32:638–646. [PubMed: 19238482]
20. Sardanelli F, Fausto A, Di Leo G, et al. In vivo proton MR spectroscopy of the breast using the total choline peak integral as a marker of malignancy. *AJR Am J Roentgenol.* 2009; 192:1608–1617. [PubMed: 19457825]
21. Laprie A, Catalaa I, Cassol E, et al. Proton magnetic resonance spectroscopic imaging in newly diagnosed glioblastoma: predictive value for the site of postradiotherapy relapse in a prospective longitudinal study. *Int J Radiat Oncol Biol Phys.* 2008; 70:773–781. [PubMed: 18262090]
22. Mueller-Lisse UG, Scherr MK. Proton MR spectroscopy of the prostate. *Eur J Radiol.* 2007; 63:351–360. [PubMed: 17709223]
23. Lichy MP, Bachert P, Hamprecht F, et al. Application of (1)H MR spectroscopic imaging in radiation oncology: choline as a marker for determining the relative probability of tumor progression after radiation of glial brain tumors. *Rofo.* 2006; 178:627–633. [PubMed: 16703499]

24. Li CW, Kuo YC, Chen CY, et al. Quantification of choline compounds in human hepatic tumors by proton MR spectroscopy at 3 T. *Magn Reson Med*. 2005; 53:770–776. [PubMed: 15799049]
25. Pucar D, Koutcher JA, Shah A, et al. Preliminary assessment of magnetic resonance spectroscopic imaging in predicting treatment outcome in patients with prostate cancer at high risk for relapse. *Clin Prostate Cancer*. 2004; 3:174–181. [PubMed: 15636684]
26. Wu B, Peng WJ, Wang PJ, et al. In vivo ^1H magnetic resonance spectroscopy in evaluation of hepatocellular carcinoma and its early response to transcatheter arterial chemoembolization. *Chin Med Sci J*. 2006; 21:258–264. [PubMed: 17249202]
27. Kuo YT, Li CW, Chen CY, et al. In vivo proton magnetic resonance spectroscopy of large focal hepatic lesions and metabolite change of hepatocellular carcinoma before and after transcatheter arterial chemoembolization using 3.0-T MR scanner. *J Magn Reson Imaging*. 2004; 19:598–604. [PubMed: 15112309]
28. Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer*. 2009; 115:616–623. [PubMed: 19117042]
29. Mannelli L, Kim S, Hajdu CH, et al. Assessment of tumor necrosis of hepatocellular carcinoma after chemoembolization: diffusion-weighted and contrast-enhanced MRI with histopathologic correlation of the explanted liver. *AJR Am J Roentgenol*. 2009; 193:1044–1052. [PubMed: 19770328]
30. Zhao WD, Guan S, Zhou KR, et al. In vivo detection of metabolic changes by ^1H -MRS in the DEN-induced hepatocellular carcinoma in Wistar rat. *J Cancer Res Clin Oncol*. 2005; 131:597–602. [PubMed: 15991046]
31. Fischbach F, Schirmer T, Thormann M, et al. Quantitative proton magnetic resonance spectroscopy of the normal liver and malignant hepatic lesions at 3.0 tesla. *Eur Radiol*. 2008; 18:2549–2558. [PubMed: 18491103]
32. Bakken IJ, Gribbestad IS, Singstad TE, et al. External standard method for the in vivo quantification of choline-containing compounds in breast tumors by proton MR spectroscopy at 1.5 tesla. *Magn Reson Med*. 2001; 46:189–192. [PubMed: 11443726]
33. Bolan PJ, Meisamy S, Baker EH, et al. In vivo quantification of choline compounds in the breast with ^1H MR spectroscopy. *Magn Reson Med*. 2003; 50:1134–1143. [PubMed: 14648561]
34. Baik HM, Su MY, Yu H, et al. Quantification of choline-containing compounds in malignant breast tumors by ^1H MR spectroscopy using water as an internal reference at 1.5 T. *MAGMA*. 2006; 19:96–104. [PubMed: 16779565]

FIGURE 1.

Diffusion-weighted MRI results. A, ADC before and after treatment. Most tumors showed an increase in ADC values 1 to 2 months after treatment. B, Change in ADC by response to treatment according to RECIST. A larger increase in tumor ADC values can be observed among responders.

FIGURE 2.

Apparent diffusion coefficient maps of a 56-year-old male patient with HCC. The upper row shows the ADC maps; the lower row shows the corresponding contrast-enhanced MR images. A, ADC map before treatment. The lesion had a mean ADC of 1.334×10^{-3} mm/s (white arrow). B, ADC map 6 weeks after TACE. The lesion had a mean ADC of 1.746×10^{-3} mm/s (white arrow).

FIGURE 3.

Proton magnetic resonance spectroscopy results. A, Choline level before and after treatment: The choline content of most tumors decreased after treatment. B, Change in choline by response to treatment according to RECIST. The decrease in choline content after treatment was larger among responders. Cho indicates choline content.

FIGURE 4.

Case 1 shows a (B) slightly decreased Choline peak after treatment compared to (A) before.

FIGURE 5.

Case 2 shows (B) strongly reduced Choline peak after treatment compared to (A) before. Choline is hardly detectable on the right spectrum.

TABLE 1**Criteria Used to Assess Response to Locoregional Therapy**

Criteria	Category	Assessment	Group
RECIST	Complete response	Disappearance of all target lesions	Responders
	Partial response	Decrease 30% in the sum of the greatest dimension of target lesions	
	Progressive disease	Increase 20% in the sum of the greatest dimension of target lesions or the appearance of new lesions	Nonresponders
	Stable disease	All other cases	
EASL	Complete response	Complete disappearance of all known disease	Responders
	Partial response	50% Reduction in viable tumoral area of all measurable lesions via uptake of contrast	Nonresponders
	Progressive disease	25% increase in viable tumoral area of all measurable lesions via uptake of contrast	
	Stable disease	All other cases	

ESL indicates European association for the study of the Liver; RECIST, Response evaluation criteria in solid tumors.

TABLE 2**Tumor Characteristics—Before Treatment**

Tumor Type	HCC	NET	CR	CCC	Other*
n (%)	29 (66)	4 (9)	4 (9)	4 (9)	3 (7)
Tumor size					
Largest diameter, median (IQR), cm	6 (4.45 – 9.33)				
Largest axial area, median (IQR), cm ²	31.64 (15.11 – 70.40)				
Choline, median (IQR), mmol/kg	4.965 (0.89 – 13.84)				
ADC, median (IQR), $\times 10^{-3}$ mm ² /s	1.472 (1.267 – 1.857)				

* Other metastasis.

NET indicates neuroendocrine metastasis; CR, colorectal cancer metastasis; CCC, cholangiocarcinoma.

TABLE 3

Tumor Characteristics Early After Therapy Group According to RECIST

RECIST Category at 6 mo	Overall n = 44	Partial Response n = 20	Stable Disease n = 21	Progressive Disease n = 3
ADC, median (IQR), $\times 10^{-3} \text{ mm}^2/\text{s}$	1.54 (1.36–1.82)	1.63 (1.45–1.98)	1.43 (1.32–1.73)	1.43 (1.24–1.58)
Change [*] in ADC, median (IQR), $\times 10^{-3} \text{ mm}^2/\text{s}$	0.093 (0.29 to –0.05)	0.05 (0.51 to –0.05)	0.11 (0.23 to –0.02)	–0.03 (0.30 to –0.61)
Choline, median (IQR), mmol/kg	0 (0–5.14)	0 (0–8.43)	1.44 (0–4.73)	0 (0–5.31)
Change [*] in choline, median (IQR), mmol/kg	–1.93 (–0 to –8.59)	–3.90 (–0 to –10.84)	–1.19 (0 to –7.09)	0 (5.31 to –9.43)

* Change = post-TACE value – pre-TACE value.

TABLE 4

Tumor Characteristics Early After Therapy Group According to EASL

EASL Category at 6 mo	Overall n = 44	Partial Response n = 29	Stable Disease n = 14	Progressive Disease n = 1
ADC, median (IQR), $\times 10^{-3}$ mm ² /s	1.54 (1.36–1.82)	1.58 (1.37–1.89)	1.45 (1.29–1.81)	1.43
Change [*] in ADC, median (IQR), $\times 10^{-3}$ mm ² /s	0.093 (0.29 to –0.05)	0.164 (0.32–0.03)	–0.005 (0.1 to –0.13)	–0.61
Choline, median (IQR), mmol/kg	0 (0–5.14)	0 (0–6.33)	1.10 (0–4.73)	5.31
Change [*] in choline, median (IQR), mmol/kg	–1.93 (0 to –8.59)	–4.99 (–1.39 to –13.14)	0 (1.80 to –1.18)	5.31

* Change = post-TACE value – pre-TACE value.