Hepatobiliary & Pancreatic Diseases International 18 (2019) 354–359

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Liver

Potential of Gd-EOB-DTPA as an imaging biomarker for liver injury estimation after radiation therapy☆

Xiao-Li Sun[a], Xue Jiang[a], Yu Kuang[b], Lei Xing[c], Lu-Yi Bu[a], Shuang-Hu Yuan[d], Jin-Ming Yu[d], Shu-Sen Zheng[e,*]

[a] *Department of Radiation Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[b] *Medical Physics Program, University of Nevada, Las Vegas, NV 89154, USA*
[c] *Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305, USA*
[d] *Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan 250117, China*
[e] *Key Laboratory of Combined Multi-organ Transplantation, Ministry of Public Health, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*

ARTICLE INFO

Article history:
Received 31 January 2019
Accepted 20 March 2019
Available online 20 May 2019

Keywords:
MRI biomarker
Radiation-induced liver disease
Liver carcinoma

ABSTRACT

Background: Hepatic radiation injury severely restricts irradiation treatment for liver carcinoma. The purpose of this study was to investigate the clinical application of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI (EOB-MRI) in the assessment of liver function after external radiation therapy and to determine the relationship between focal liver reaction (FLR) and liver function.

Methods: A total of 47 patients with liver malignancies who underwent external beam radiation therapy were enrolled. EOB-MRI was performed on each patient at approximately one month post-radiotherapy. The hepatobiliary (HPB) phase images from EOB-MRI were fused with the planning CT images, and the isodose lines from the patients' treatment plans were overlaid onto the fused images. The correlation of the EOB-MR image intensity distribution with the isodose lines was studied. We also compared liver function in patients between pre-treatment and post-treatment.

Results: Decreased uptake of Gd-EOB-DTPA, which was manifested by well-demarcated focal hypointensity of the liver parenchyma or FLR to high-dose radiation, was observed in the irradiated areas of 38 patients. The radiotherapy isodose line of decreased uptake area of Gd-EOB-DTPA was 30–46 Gy. The median corresponding dose curve of FLR was 34.4 Gy. Nine patients showed the absence of decreased uptake area of Gd-EOB-DTPA in the irradiated areas. Compared to the 38 patients with the presence of decreased uptake area of Gd-EOB-DTPA, 9 patients with the absence of decreased uptake area of Gd-EOB-DTPA showed significant higher levels of total bile acid, total bilirubin, direct bilirubin and alpha-fetoprotein ($P < 0.05$). There were no significant differences in alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase or albumin levels between the two groups ($P > 0.05$).

Conclusions: Visible uptake of Gd-EOB-DTPA by the liver parenchyma was significantly associated with liver function parameters. EOB-MRI can be a valuable imaging biomarker for the assessment of liver parenchyma function outside of radiation area.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer-related death [1]. Radiotherapy is a viable treatment option for locally advanced, unresectable HCC and liver metastasis, either alone or as part of combined therapy. However, radiation-induced liver disease (RILD) presents a clinical challenge when dose escalation is required to determine optimal HCC treatment. RILD can even lead to significant morbidity and mortality [2,3]. RILD typically occurs in 4–8 weeks after completion of radiotherapy, initially presenting as abnormal liver function, and no effective management of this complication has been identified as of yet. Computed tomography

☆ *Part of this study was presented in American Society for Radiation Oncology (ASTRO) Annual Meeting on September 25–28, 2016 at Boston, USA.*

* Corresponding author.
E-mail address: shusenzheng@zju.edu.cn (S.-S. Zheng).

https://doi.org/10.1016/j.hbpd.2019.05.005

(CT) is routinely used to monitor radiation-induced changes such as focal liver reaction (FLR) [4,5]. However, CT has limited sensitivity for the density change of liver tissue. Furthermore, an intensity change on CT images does not necessarily reflect a change in liver function. Therefore, it is necessary to develop an effective functional imaging to determine the overall liver function after radiation.

Recently, MRI using a special contrast agent, gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DTPA), which is taken up specifically by hepatocytes, has attracted research attention. Gd-EOB-DTPA has the ability to identify and characterize HCC and to measure hepatocyte function. After intravenous injection, Gd-EOB-DTPA is preferentially absorbed by hepatocytes and eventually excreted via the biliary pathway [6–8]. Some preliminary studies have been conducted to visualize hepatocyte injury in patients with HCC after radiotherapy using Gd-EOB-DTPA-enhanced MRI (EOB-MRI). These studies suggest that hypointense areas on EOB-MR images could be used to identify FLR [3,9,10]. However, there is still limited knowledge regarding the relationship between FLR observed on EOB-MR images and liver function.

Based on the clinical consensus, RILD may occur in some patients within 1 month without any clinical symptoms. Therefore, performing an EOB-MRI scan at one month post-treatment may help clinicians identify RILD in a timely manner. Moreover, patients with liver tumor are often given local boosts of radiotherapy to start the treatment. This study aimed to investigate the clinical application of EOB-MRI as an imaging biomarker for the assessment of liver function after external beam radiation and to determine the relationship between FLR and liver function.

Methods

Patients

Forty-seven patients with primary or secondary liver malignancies treated by radiotherapy between July 2013 and September 2018 were included in this analysis. All enrolled patients met the following criteria: 1) with primary or secondary liver malignancies; 2) liver function is Child-Pugh grade A or B; 3) the follow-up data of liver function was available; and 4) EOB-MRI data were approximately one month after radiotherapy.

This study was conducted in accordance with *the Declaration of Helsinki* of 1975, as revised in 2000 and 2008. The study protocol was approved by the Ethics Committee of the First Hospital of Zhejiang University School of Medicine (approval number 2013-167). Written informed consents were obtained from all patients.

Radiotherapy

The CT scans were performed under breath holding at full expiration. The gross volume of the liver tumor was contoured according to the region of the tumor shown on pre-radiotherapy MR images. An individualized treatment margin of 5–8 mm was applied to determine the target volume. The radiotherapy dose was delivered using 6–10 MV photons in a linear accelerator (Trilogy, Varian Medical Systems Inc., Palo Alto, CA, USA) over 5 days per week. Treatment was to cover the target volume by the 90% isodose line of the maximum dose.

Post-radiotherapy EOB-MRI

Patients underwent EOB-MRI one month after completion of radiotherapy. The dose of Gd-EOB-DTPA (Primovist, Bayer Healthcare, Osaka, Japan) administered was 0.1 mL/kg (0.05 mmol/kg). The scans were performed using a 3.0 T MRI scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany).

The SENSE body coil was used for image acquisition. The hepatobiliary (HPB) phase of EOB-MR images was obtained 20 min post-injection of Gd-EOB-DTPA using axial three-dimensional T1-high resolution isotropic volume excitation with the following acquisition parameters: breath holding, flip angle = 20°, slice thickness = 4 mm, field of view = 360 × 270, repetition time/echo time = 3/1 ms, SENSE factor = 1.3, selective partial inversion recovery, matrix size of 224 × 116, bandwidth = 995 Hz/pixel, centric ordering of k space and acquisition time = 22 s. FLR was evaluated in the HPB region. The liver parenchyma in the irradiated area showed a low signal intensity, which was defined as a "hypointense area" by two experienced radiologists based on clinical consensus. The border of hypointense areas within the HPB region was consistently delineated by the radiologists.

Fusion of EOB-MR images and CT images

The HPB regions were further evaluated using MIM Maestro v6.4.5 (MIM Software, Cleveland, OH, USA) on a computer workstation by two experienced radiologists. The decreased uptake areas on the EOB-MR images were identified as the FLRs. The border of decreased uptake area within the HPB region was consistently delineated. The HPB images were then fused to the CT images with the dose distribution using the auto-registration function in the Eclipse radiation therapy treatment planning system (Varian Medical Systems Inc.). The isodose line coinciding with the distance to the border of the hypointense area delineated on the EOB-MR images was recorded as the "corresponding dose curve (CDC) of FLR". All MR images were delineated in the HPB phase by two experienced abdominal radiologists (SXL and JX) based on clinical consensus. If these two radiologists were inconsistent, the third senior radiologist (YSH) was invited to judge the images in question.

Evaluation of liver function and follow-up

All patients had weekly follow-up during radiotherapy and at one day prior to EOB-MRI. Weekly follow-up included physical examinations and laboratory measurements of albumin (ALB), globulin (GLB), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and total bile acid (TBA) levels. All of the parameters were measured using a conventional automated analyser (Beckman Au680, USA). Hepatic toxicity was defined according to the Common Terminology Criteria (CTC, Version 4) of the National Cancer Institute. No patient had evidence of liver dysfunction prior to radiotherapy.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Continuous data that conformed to the normal distribution were described as the mean ± standard deviation (± SD), and an independent sample *t*-test was used for comparisons between groups. Continuous data of non-normally distributed data are described by the median and interquartile range (IQR), and the Mann–Whitney *U* test was used for comparison between groups. A $P < 0.05$ was considered statistically significant.

Results

During the radiation treatment, 43 patients had acute hepatic toxicity with CTC grade 1, and 4 patients had CTC grade 2. Six patients had acute gastrointestinal complications. Forty-five patients recovered from the toxicity after symptomatic treatments and finished the initial treatment plan. Two patients, who almost finished their treatment plan but had to discontinue irradiation

Table 1
Characteristics of patients ($n = 47$).

Characteristics	Values
Sex (male/female)	30/17
Median age (yr)	65 (54–70)
Median tumor size (cm)	5.8 (3.4–8.1)
Tumor position (central/peripheral)	16/31
Child-Pugh classification (A/B)	43/4
HBV infection (+/−)	24
HCV infection (+/−)	7
TACE (+/−)	16/31
Chemotherapy (+/−)	18/29
Liver resection (+/−)	11/36
HCC/liver metastases	21/26

HBV: hepatitis B virus; HCV: hepatitis C virus; TACE: transarterial chemoembolization; HCC: hepatocellular carcinoma.

Table 2
Radiotherapy factors.

Factors	Median (IQR)
Liver volume (mL)	1164.5 (903.5–1246.6)
GTV (mL)	140.6 (40.4–180.5)
PTV (mL)	235.6 (69.7–286.7)
Total dose (Gy)	49.8 (32.2–54.0)
Fraction	16.2 (10.0–24.0)
BED10 (Gy)	72.2 (63.3–85.0)
BED2 (Gy)	114 (92.3–125.8)
V5*	70.6% (35.8%–75.8%)
V20	28.4% (18.3%–52.3%)
V35	12.8% (9.9%–24.5%)
Mean liver dose (Gy)	17.6 (10.7–25.1)
CDC of FLR (Gy)	34.4 (32.1–44.9)

* V5 is the percentage of normal liver volume that received 5 Gy in the total normal liver volume. The other V with suffixes express the same meaning, and the numbers represent the doses received. GTV: gross tumor volume; PTV: planning target volume; BED: biological effective *dose*; CDC: corresponding dose curve; FLR: focal liver reaction; BED10: biological effective dose when $\alpha/\beta = 10.0$; BED2: biological effective dose when $\alpha/\beta = 2.0$.

due to the worsened general conditions, were still included in the analyses because the prescription doses were delivered completely (Table 1).

Patients underwent EOB-MRI at a median of 35 days (IQR: 30–45) after the last day of radiotherapy. Of these, 31 received three-dimensional conformal radiotherapy (3D-CRT), and 16 were treated by stereotactic body radiotherapy (SBRT). The median total irradiation time was 18 days (IQR: 10–40). Mean liver dose was 27.6 Gy (IQR: 10.7–31.1), and total dose was 49.8 Gy (IQR: 32.2–54.0). The radiotherapy parameters are summarized in Table 2.

The EOB-MR images revealed hypointense regions in the irradiated areas of 38 patients. In each case, there was an overlap between the irradiated volume and the decreased uptake area of Gd-EOB-DTPA in the HPB phase of EOB-MR images. The median distance between the isodose curve and the border of the hypointense areas on EOB-MR images was 1.4 mm (IQR: 0.8–2.0). The corresponding isodose lines ranged from 30 to 46 Gy (Table 2). The median corresponding dose curve of FLR was 34.4 Gy in these 38 patients. Nine patients had the absence of decreased uptake area of Gd-EOB-DTPA irradiated areas.

A representative case of the planned dose distribution overlaid on the EOB-MRI was shown in Fig. 1. The hypointense area coinciding with the isodose line of 42.4 Gy is clearly shown in Fig. 1D. In contrast, no enhancement was observed in the region that received a lower dose. In this patient, a homogenous, hypointense signal distribution was observed (Fig. 1C).

Compared to patients with the presence of decreased uptake area of Gd-EOB-DTPA in the irradiated areas, those with the absence of decreased uptake area of Gd-EOB-DTPA showed significantly higher levels of TBA, TBIL and DBIL ($P < 0.05$). Alpha-fetoprotein (AFP) levels were lower in patients with the presence of decreased uptake area of Gd-EOB-DTPA than in those with the absence of decreased uptake area of Gd-EOB-DTPA ($P < 0.05$). In addition, there were no significant differences in ALT, AST, GGT or ALB levels between these two groups ($P > 0.05$, Table 3).

Table 3
Comparison of the liver function parameters between patients with the presence/absence of decreased uptake area of EOB-MRI.

Parameters	Presence of decreased uptake ($n = 38$)	Absence of decreased uptake ($n = 9$)	*P* value
ALT (U/L)	30.6 ± 16.3	40.4 ± 13.9	0.139
AST (U/L)	29.4 ± 17.9	37.4 ± 10.9	0.067
TBA (μmol/L)	9.8 (6.40–12.70)	15.5 (10.0–17.4)	**0.020**
TBIL (μmol/L)	14.0 (6.2–19.9)	18.3 (15.5–23.5)	**0.033**
DBIL (μmol/L)	2.8 (2.5–4.3)	5.3 (3.6–5.9)	**0.035**
GGT (U/L)	32.1 (12.7–38.2)	38.6 (17.50–46.00)	0.519
ALB (g/L)	41.2 (36.5–48.1)	46.2 (41.3–49.3)	0.647
AFP (μg/L)	328.7 (109.3–850.5)	699.1 (188.5–1133.9)	**0.013**

Gd-EOB-DTPA: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; ALT: alanine transaminase; AST: aspartate aminotransferase; TBA: total bile acid; TBIL: total bilirubin; DBIL: direct bilirubin; GGT: gamma-glutamyl transpeptidase; ALB: albumin; AFP: alpha-fetoprotein.

Discussion

Surveillance following radiotherapy for liver tumors is challenging because of the uncertainties concerning the use of existing imaging technology for clinical decision-making. Radiographic changes in the liver after radiotherapy have been observed in several imaging studies [11–13]. For example, clinically transient decreases in CT-defined tissue density can be observed 2–3 months after radiotherapy. Sometimes these changes are visible on CT as sharply demarcated areas corresponding to radiation portals, which can be misinterpreted as tumor progression or irreversible liver injury [14]. Therefore, a sensitive and quantitative technique is needed because the change in intensity on CT images does not accurately reflect the inherent radiosensitivity of hepatocytes or the functional units of the liver [15].

EOB-MRI can be used to show hepatocyte function, to characterize radiographic changes in the HPB phase and to identify well-demarcated focal parenchymal changes [16–18]. Therefore, this imaging technique holds promise to improve the management of patients with liver tumors. However, to the best of our knowledge, despite the increasing evidence suggesting that EOB-MRI could be used to detect HCC [19,20], there have been no reports on the potential clinical application of EOB-MRI for the assessment of liver function after external beam radiation therapy or the use of EOB-MRI to determine the relationship between FLR and liver function.

Our EOB-MRI study demonstrated clear radiologic changes in 38 of 47 patients. The hypointense regions on the EOB-MR images correlated well with areas that had received high-dose irradiation. The radiographic images showed fair matching of the decrease in Gd-EOB-DTPA uptake by hepatocytes in the irradiated areas.

The molecular mechanisms of contrast uptake and excretion have been investigated. Richter et al. measured the expression of specific transport proteins and related cytokines in blood and biopsy-derived tissue samples and found that the results were correlated with the findings on MRI, which they believed could explain individual variations in decreased MRI signals [21]. It has been suggested that the organic anion transporting polypeptide (OATP) -8 and OATP-2 transporter proteins located at the apical

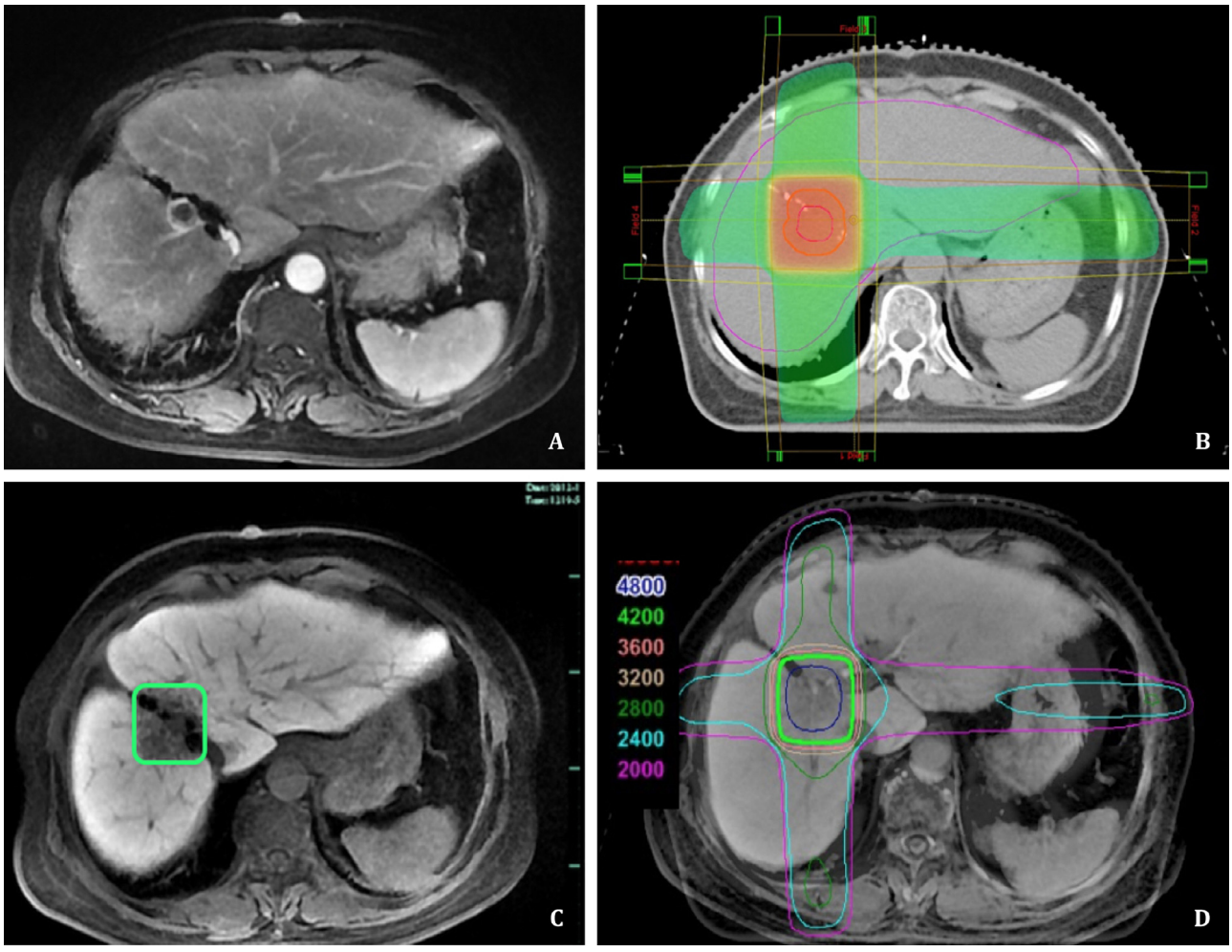

Fig. 1. Images of a 64-year-old woman with hepatocellular carcinoma who underwent radiotherapy. **A**: A tumor measuring 2.4 cm in diameter was observed on pre-treatment MRI; **B:** The radiotherapy prescription for the target lesion was a combination of four fields of 50 Gy in 25 fractions (biological effective dose: 60 Gy). EOB-MRI was performed on day 35 after the end of radiotherapy; **C**: The irradiated area clearly shows the presence of decreased uptake area of Gd-EOB-DTPA. A hypointense area within the irradiated region was observed. The outline of the hypointense area was drawn by the physician (thick green line); **D**: The isodose line corresponding to the outline of the hypointense area was 42.4 Gy (BED of 50.4 Gy) on the fused image. Gd-EOB-DTPA: gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid; MRI: magnetic resonance imaging.

membrane of hepatocytes may facilitate the uptake area of Gd-EOB-DTPA in functioning hepatocytes. Exposure to radiation could decrease the expression of these transporter proteins and up-regulate the expression of excretion proteins, leading to a decrease in signal intensity in HPB areas [22]. More recently, studies have demonstrated a strong association between the expression of OATP-1B3 and the transport of gadoxetic acid into liver cancer cells [23–25]. However, the molecular mechanism of this process is still under investigation.

The correlation between radiation dose and changes in signal intensity on MRI has been investigated in previous studies. Okamoto et al. [3] suggested that a threshold of 29–35 Gy is needed to delineate the liver parenchyma after irradiation. Sanuki et al. [10] identified an isodose line of 35 Gy as the threshold corresponding to the periphery of the planning target volume after SBRT. Moreover, Nishie et al. [26] reported that the threshold for identification of decreased uptake area of Gd-EOB-DTPA on MRI was 36–40.5 Gy. Our present results are consistent with those of previous reports in that isodose lines in the range of 30–46 Gy coincided with the decreased uptake areas of Gd-EOB-DTPA.

In our study, nine patients with blur demarcated lesion under EOB-MRI had higher levels of TBA, TBIL and DBIL compared to those with well-demarcated lesion. Higher levels of TBA, TBIL and DBIL reflect hepatocyte damage or bile duct obstruction. Furthermore, Gd-EOB-DTPA is only uptaken by functional hepatocytes Therefore, we attribute the poor Gd-EOB-DTPA uptake to the poor liver function in our 9 cases. After the Gd-EOB-DTPA administration, the hepatocytes in the radiation area lost their function and therefore, showed hypointensity. Furthermore, if the hepatocytes next to the radiation area have poor function, these cells also cannot absorb Gd-EOB-DTPA and therefore, the contrast border between radiation area and the surrounding parenchyma is not clear. If the hepatocytes have function, these hepatocytes will absorb Gd-EOB-DTPA after administration and therefore, the border between radiation area and the surrounding parenchyma is clear. These 9 patients also had higher AFP levels than those with well-demarcated lesions, which suggested a large tumor burden in these patients. Studies in the rodent liver failed to show a decrease in Gd-EOB-DTPA uptake in 3 days after irradiation with a dose of 50–70 Gy, suggesting that information on RILD provided by EOB-MRI may require an optimal imaging time point [23,27]. The volume of FLR has been reported to change over time in HCC patients as a result of repair and regeneration [28]. Sanuki et al. [10] determined Child-Pugh score was the only parameter that predicted potential loss of liver tissue in EOB-MRI which generally occurred 3 months after radiotherapy. Our study selected EOB-MRI data of one month

after radiotherapy, and we demonstrated that potential RILD is detectable in one month after radiotherapy.

Bae et al. [29] attributed poor Gd-EOB-DTPA uptake in patients with chronic liver disease to regional decreases in function within the liver. Kobayashi et al. [30] also reported that the tolerance of hepatocytes to radiation was decreased in patients with cirrhosis or chronic hepatitis. Our results are fairly consistent with those previous studies reporting that liver function is preserved in patients with HBV and HCV who undergo radiotherapy [31–33].

The main limitation of this study was that the pathological data and the correlation of pathological data with imaging findings were not available, mainly because all the patients had inoperable liver tumors. It would be useful in future research to enroll patients who are candidates for both radiotherapy and surgery so that a correlative investigation could be performed.

In conclusion, decisions regarding treatment with liver radiotherapy often aim for an acceptable balance between the potential efficacy and toxicity of treatment. EOB-MRI can identify FLR through decreased uptake area of Gd-EOB-DTPA, thus providing a potentially useful imaging biomarker for therapeutic assessment. This study showed a correlation between regions visible on liver EOB-MRI and laboratory parameters of liver function and presented a valuable imaging biomarker for liver radiotherapy. These radiographic changes are potentially useful for the prediction of RILD, which can be used to decide whether a boost in radiation dose should be prescribed in the clinical setting.

Contributors

XL, YJM and ZSS designed the project. SXL and JX collected and analyzed the data. BLY designed the radiotherapy plan. YSH analyzed the data. SXL and KY wrote the paper. KY and XL revised the paper. SXL and JX contributed equally to this work. ZSS is the guarantor.

Funding

This work was supported by grants from the Project of Health Commission of Zhejiang province (2014KYA075) and Natural Science Foundation of Zhejiang province (2014C33199).

Ethical approval

The study protocol was approved by the ethics committee at the First Hospital of Zhejiang University School of Medicine (approval number 2013-167).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol 2016;34:1787–1794.
[2] Guha C, Kavanagh BD. Hepatic radiation toxicity: avoidance and amelioration. Semin Radiat Oncol 2011;21:256–263.
[3] Okamoto D, Nishie A, Asayama Y, Tajima T, Ishigami K, Kakihara D, et al. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MR finding of radiation-induced hepatic injury: relationship to absorbed dose and time course after irradiation. Magn Reson Imaging 2014;32:660–664.
[4] Collettini F, Poellinger A, Schnapauff D, Denecke T, Wust P, Braicu IE, et al. CT-guided high-dose-rate brachytherapy of metachronous ovarian cancer metastasis to the liver: initial experience. Anticancer Res 2011;31:2597–2602.
[5] Collettini F, Schnapauff D, Poellinger A, Denecke T, Schott E, Berg T, et al. Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of large (5–7cm) and very large (>7cm) tumours. Eur Radiol 2012;22:1101–1109.
[6] Narita M, Hatano E, Arizono S, Miyagawa-Hayashino A, Isoda H, Kitamura K, et al. Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. J Gastroenterol 2009;44:793–798.
[7] Zech CJ, Vos B, Nordell A, Urich M, Blomqvist L, Breuer J, et al. Vascular enhancement in early dynamic liver MR imaging in an animal model: comparison of two injection regimen and two different doses Gd-EOB-DTPA (gadoxetic acid) with standard Gd-DTPA. Invest Radiol 2009;44:305–310.
[8] Takeyama Y, Tsuchiya N, Kunimoto H, Fukunaga A, Sakurai K, Hirano G, et al. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging as a useful detection method for advanced primary biliary cirrhosis. Hepatol Res 2015;45:E108–E114.
[9] Seidensticker M, Seidensticker R, Mohnike K, Wybranski C, Kalinski T, Luess S, et al. Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: tolerance dose of small liver volumes. Radiat Oncol 2011;6:40.
[10] Sanuki N, Takeda A, Oku Y, Eriguchi T, Nishimura S, Aoki Y, et al. Threshold doses for focal liver reaction after stereotactic ablative body radiation therapy for small hepatocellular carcinoma depend on liver function: evaluation on magnetic resonance imaging with Gd-EOB-DTPA. Int J Radiat Oncol Biol Phys 2014;88:306–311.
[11] Sanuki N, Takeda A, Mizuno T, Oku Y, Eriguchi T, Iwabuchi S, et al. Tumor response on CT following hypofractionated stereotactic ablative body radiotherapy for small hypervascular hepatocellular carcinoma with cirrhosis. AJR Am J Roentgenol 2013;201:W812–W820.
[12] Huang WY, Kao CH, Huang WS, Chen CM, Chang LP, Lee MS, et al. 18F-FDG PET and combined 18F-FDG-contrast CT parameters as predictors of tumor control for hepatocellular carcinoma after stereotactic ablative radiotherapy. J Nucl Med 2013;54:1710–1716.
[13] Brook OR, Thornton E, Mendiratta-Lala M, Mahadevan A, Raptopoulos V, Brook A, et al. CT imaging findings after stereotactic radiotherapy for liver tumors. Gastroenterol Res Pract 2015;2015:126245.
[14] Yamasaki SA, Marn CS, Francis IR, Robertson JM, Lawrence TS. High-dose localized radiation therapy for treatment of hepatic malignant tumors: CT findings and their relation to radiation hepatitis. AJR Am J Roentgenol 1995;165:79–84.
[15] Geisel D, Lüdemann L, Hamm B, Denecke T. Imaging-based liver function tests–past, present and future. Rofo 2015;187:863–871.
[16] Esterson YB, Flusberg M, Oh S, Mazzariol F, Rozenblit AM, Chernyak V. Improved parenchymal liver enhancement with extended delay on Gd-EOB-DTPA-enhanced MRI in patients with parenchymal liver disease: associated clinical and imaging factors. Clin Radiol 2015;70:723–729.
[17] Faletti R, Cassinis MC, Fonio P, Bergamasco L, Pavan LJ, Rapellino A, et al. Multiparametric Gd-EOB-DTPA magnetic resonance in diagnosis of HCC: dynamic study, hepatobiliary phase, and diffusion-weighted imaging compared to histology after orthotopic liver transplantation. Abdom Imaging 2015;40:46–55.
[18] Ichikawa T, Sano K, Morisaka H. Diagnosis of pathologically early HCC with EOB-MRI: experiences and current consensus. Liver Cancer 2014;3:97–107.
[19] Kobi M, Paroder V, Flusberg M, Rozenblit AM, Chernyak V. Limitations of GD-EOB-DTPA-enhanced MRI: can clinical parameters predict suboptimal hepatobiliary phase? Clin Radiol 2017;72:55–62.
[20] Liang M, Zhao J, Xie B, Li C, Yin X, Cheng L, et al. MR liver imaging with Gd-EOB-DTPA: the need for different delay times of the hepatobiliary phase in patients with different liver function. Eur J Radiol 2016;85:546–552.
[21] Richter C, Seco J, Hong TS, Duda DG, Bortfeld T. Radiation-induced changes in hepatocyte-specific Gd-EOB-DTPA enhanced MRI: potential mechanism. Med Hypotheses 2014;83:477–481.
[22] Hidaka M, Takatsuki M, Okudaira S, Soyama A, Muraoka I, Tanaka T, et al. The expression of transporter OATP2/OATP8 decreases in undetectable hepatocellular carcinoma by Gd-EOB-MRI in the explanted cirrhotic liver. Hepatol Int 2013;7:655–661.
[23] Shimizu A, Kobayashi A, Motoyama H, Sakai H, Yamada A, Yoshizawa A, et al. Features of acute liver congestion on gadoxetate disodium-enhanced MRI in a rat model: role of organic anion-transporting polypeptide 1A1. J Magn Reson Imaging 2015;42:828–836.
[24] Yoneda N, Matsui O, Ikeno H, Inoue D, Yoshida K, Kitao A, et al. Correlation between Gd-EOB-DTPA-enhanced MR imaging findings and OATP1B3 expression in chemotherapy-associated sinusoidal obstruction syndrome. Abdom Imaging 2015;40:3099–3103.
[25] Kimura Y, Sato S, Hitomi E, Ohyama M, Adachi K, Inagaki Y, et al. Coexpression of organic anion-transporting polypeptides 1B3 and multidrug-resistant proteins 2 increases the enhancement effect of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid on hepatocellular carcinoma in magnetic resonance imaging. Hepatol Res 2014;44:327–337.
[26] Nishie A, Ushijima Y, Tajima T, Asayama Y, Ishigami K, Kakihara D, et al. Quantitative analysis of liver function using superparamagnetic iron oxide- and Gd-EOB-DTPA-enhanced MRI: comparison with Technetium-99m galactosyl serum albumin scintigraphy. Eur J Radiol 2012;81:1100–1104.
[27] Saito S, Obata A, Kashiwagi Y, Abe K, Murase K. Dynamic contrast-enhanced MRI of the liver in Mrp2-deficient rats using the hepatobiliary contrast agent Gd-EOB-DTPA. Invest Radiol 2013;48:548–553.
[28] Olsen CC, Welsh J, Kavanagh BD, Franklin W, McCarter M, Cardenes HR, et al. Microscopic and macroscopic tumor and parenchymal effects of liver stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2009;73:1414–1424.
[29] Bae KE, Kim SY, Lee SS, Kim KW, Won HJ, Shin YM, et al. Assessment of hepatic function with Gd-EOB-DTPA-enhanced hepatic MRI. Dig Dis 2012;30:617–622.

[30] Kobayashi S, Matsui O, Gabata T, Koda W, Minami T, Kozaka K, et al. Intrahepatic periportal high intensity on hepatobiliary phase images of Gd-EOB-DTPA-enhanced MRI: imaging findings and prevalence in various hepatobiliary diseases. Jpn J Radiol 2013;31:9–15.
[31] Ding Y, Rao SX, Chen C, Li R, Zeng MS. Assessing liver function in patients with HBV-related HCC: a comparison of T_1 mapping on Gd-EOB-DTPA-enhanced MR imaging with DWI. Eur Radiol 2015;25:1392–1398.
[32] Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. J Clin Oncol 2012;30:623–630.
[33] Chen JH, Chang PY, Ho CL, Chen PJ. Radiofrequency ablation as a palliative treatment of primary liver sarcoma in an inoperable patient with hepatitis C virus-related cirrhosis. Onkologie 2009;32:509–512.