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journal or publication title	博士論文本文Full
学位授与番号	13301甲第4463号
学位名	博士（保健学）
学位授与年月日	2016-09-26
URL	http://hdl.handle.net/2297/46647

Preliminary study of apparent diffusion coefficient assessment after ion beam therapy for hepatocellular carcinoma

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Received: 29 May 2015 / Revised: 21 March 2016 / Accepted: 24 March 2016 / Published online: 7 April 2016
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Abstract We evaluated the state of hepatocellular carcinoma (HCC) and the liver after ion beam therapy by analyzing the apparent diffusion coefficient (ADC). In this retrospective study, we evaluated 13 HCC lesions in 10 patients who underwent magnetic resonance imaging before and after therapy. Diffusion-weighted imaging was performed with use of b values of 0, 150, and 800 s/mm². The ADC was determined for the tumor, irradiated liver, and normal liver. The maximum size of the tumor was measured, and reduction in tumor size was determined as a ratio of the maximum size of the diameter of the tumor. We compared the ADC before and after the therapy with the reduction in tumor size ratio. The reduction in tumor size ratio was compared with the ADCs of the tumors. The ADC of the tumor and the irradiated liver were significantly higher after therapy than before therapy. The ADC of the normal liver was not significantly different before and after therapy. The reduction ratio increased significantly ($R = 0.73$, $P = 0.006$) after therapy at the second

follow-up when compared with after therapy at the first follow-up. No correlation was found between the reduction ratio and the ADC of the tumor in each follow-up. Inflammation of the liver occurs after treatment as a result of radiation doses from the ion beam, and the tumor reaches a state of necrosis. ADC value analysis provides a non-invasive assessment and yields focal information regarding the tumor and liver before and after ion beam therapy.

Keywords Hepatocellular carcinoma · Magnetic resonance imaging · Diffusion-weighted imaging · Apparent diffusion coefficient · Ion beam therapy

1 Introduction

Hepatocellular carcinoma (HCC) is one of the five main types of cancer that affect adult males worldwide [1]. Treatment options for HCC consist of surgical resection, transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and radiotherapy [2–8]. A recent study showed that low-dose radiotherapy and whole-liver irradiation were ineffective, as they led to severe hepatic failure [9]. One study suggested that localized high-dose radiation therapy can improve the efficacy of radiation therapy [8], and ion beams can provide a better dose concentration than can photon beams [10, 11]. Indeed, ion beams are considered a highly effective treatment for cancer due to their higher relative biological effectiveness (RBE) [12, 13].

The response to HCC therapy can be evaluated by measurement of changes in tumor size via a variety of diagnostic equipment. For example, dynamic contrast-enhanced computed tomography (DCE-CT) and DCE-

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magnetic resonance imaging (MRI) can be used for assessment of the presence of a hypervascular tumor in the arterial phase. However, poorly differentiated HCC shows hypovascularity with this assessment [14]. Diffusion-weighted imaging (DWI) is an MRI method that produces an image based on regional differences in the random motion of water molecules. DWI provides information different from that of T_1 -weighted imaging (T_1 WI) and T_2 -weighted imaging (T_2 WI). DWI can detect cellular edema and malignant tumors due to their relative differences in cellular density. The apparent diffusion coefficient (ADC) can be measured quantitatively in vivo based on the diffusion of tissue. Therefore, DWI provides a greater possibility of early assessment of the tumor when compared with imaging-based analysis of tumor blood flow and tumor conditions. Studies have described a number of useful ADCs for the evaluation of the response to treatment for HCC and liver metastases [15–20]. However, assessment of ADC values following ion beam therapy has not been reported previously for patients with HCC.

Our purpose in this study was to evaluate the utility of the ADC for the assessment of the response to ion beam therapy in patients with HCC and liver conditions.

2 Materials and Methods

2.1 Patients

Ten consecutively enrolled patients (eight men, two women; mean age 75.0 years; age range 58–81 years) with HCC, including 13 HCC lesions, were evaluated retrospectively from January 2008 to October 2012. Hepatitis B virus infection was noted in four patients, hepatitis C virus infection was noted in three patients, and non-alcoholic steatohepatitis (NASH) was noted in four patients. Patient demographic data including cause of lesion, size of tumor, and Child-Pugh classification are given in Table 1.

This study was approved by our medical ethics board. Informed consent was obtained from each patient at the time of enrollment. On DWI, each tumor showed a high signal intensity. On DCE-MRI with gadolinium ethoxybenzyl diethylenetriamine triamine pentaacetic acid (Gd-EOB-DTPA) (Primovist; Bayer Schering Pharma, Berlin, Germany), the tumor showed a low signal intensity in the hepatobiliary phase, a high signal intensity in the arterial phase, and a low signal intensity in the late arterial phase.

2.2 Ion beam therapy

Respiratory movement was measured by digital radiography (DAR-3000; Shimadzu). During free breathing of the patient, examinations were performed at 2–60 frames/s.

Movement was measured as an index of the diaphragm during inspiration from the time the patient began to breathe. CT treatment involved the use of multi-detector computed tomography (MDCT; Asteion TSX-021A, Toshiba Medical Inc.) and a breathing respiratory-gated infrared system synchronizer (Anzai Medical Inc.). The determination of the gross tumor volume (GTV) was performed by Gd-EOB-DTPA MRI. A particle therapy planning system (XIO; CMS Japan) was also used. The clinical target volume (CTV) and planning target volume (PTV) were defined as follows: $CTV = GTV + 5 \text{ mm}$, and $PTV = CTV + 5 \text{ mm}$ (setup margin) + 1 mm (internal margin). The margin was set by inferior respiratory displacement results obtained before respiratory movement. The radiation dose was in the range of 66–76 Gy equivalent (GyE) (mean dose 70 GyE) [21]. The ion beams were a proton beam of 150 or 210 MeV and a carbon beam of 320 MeV.

2.3 MRI technique

A 1.5-T MRI system (Gyrosan Intera; Philips Medical Systems International, Best, The Netherlands) with a sensitivity encoding (SENSE) phased array coil was used, with patients placed in the supine position. DCE-MRI and hepatobiliary-phase images were obtained during breath holding. For the DCE-MRI, a dose of 0.1 mL of Gd-EOB-DTPA per kilogram of body weight was injected intravenously at a flow rate of 2.0 mL/s, followed by a 30-mL saline flush administered at 2.0 mL/s. Unenhanced, double-arterial and portal venous equilibrium, and hepatobiliary phase images were then obtained. Images were obtained at 25, 35.5, 60, 150 s, and 20 min after injection of Gd-EOB-DTPA. DCE-MRI and hepatobiliary phase images were obtained with use of an enhanced T_1 -weighted high-resolution isotropic volume examination (e-THRIVE). The scan parameters of DCE-MRI were as follows: repetition time (TR) 4.0 ms; echo time (TE) 1.98 ms; acquisition time 1 phase = 10.5 s; matrix size 192×256 ; field of view (FOV) $270 \times 350 \text{ mm}$; number of signals averaged (NSA) 1; flip angle 12° ; slice thickness 3 mm; number of slices 70; reduction factor 1.8. The scan parameters of the hepatobiliary phase were as follows: TR 4.1 ms; TE 2.0 ms; acquisition time 20.6 s; matrix size 240×400 ; FOV $270 \times 350 \text{ mm}$; NSA 1; flip angle 12° ; slice thickness 2 mm; number of slices 100; reduction factor 1.5.

Diffusion-weighted imaging was obtained by use of respiratory-triggered single-shot echo planar imaging (EPI). The scan parameters were as follows: TR 1800 ms; TE 64 ms; acquisition time 240 s; matrix size 112×256 ; FOV $270 \times 350 \text{ mm}$; NSA 3; flip angle 90° ; slice thickness 5 mm; slice gap 0.5 mm; number of slices 30; reduction factor 2.0; b value 0, 150 and 800 s/mm^2 .

Table 1 Patient characteristics

Patient number	Size of tumor base line (mm)	Size at first follow-up (mm)	Size at second follow-up (mm)	Segment no.	Child-Pugh class
1	18.75	10.94	6.25	S6	A
2	26.05	14.58	9.70	S4	B
3	47.54	28.70	24.3	S3	A
4	37.70	10.80	7.58	S7	A
	9.17	5.47	3.40	S8	
	26.43	9.00	7.10	S8	
5	16.00	11.10	7.00	S8	A
	10.17	6.50	5.60	S7	
6	22.10	20.80	9.11	S8	B
7	33.72	29.38	25.42	S6	A
8	27.36	13.71	9.20	S6	A
9	22.36	18.33	14.43	S6	A
10	21.87	13.26	10.98	S8	A

2.4 Image analysis and selection of regions of interest

The ADC maps were calculated for b values of 150 and 800 s/mm². The regions of interests (ROIs) in the ADC maps were delineated as tumor, normal irradiated liver, and normal non-irradiated liver. The ROI created on the trace in the tumor included the whole tumor for all high-signal areas on lesions referred to as DCE-MRI and a b value of 800 s/mm² (Fig. 1). The ADC of each tumor was then measured. The ROI of the irradiated liver was delineated at

about 50 % (35 GyE) of the prescription dose. Because the dose distribution is steeper according to the Bragg peak, the ROIs of the irradiated liver and of the normal liver were set at approximately 1 cm in diameter within the right lobe so that vessels and tumor lesions were avoided. The ROIs created on the trace images were copied and pasted onto the ADC map by use of the MR system. Each ADC was measured three times. The diameter of the tumor was measured as the largest diameter at each examination time in DCE-MRI. The tumor reduction ratio was defined as follows:

Fig. 1 A 60-year-old man with hepatocellular carcinoma (HCC) of segment VII (arrows) before ion beam therapy. **a** T₁-weighted high-resolution isotropic volume examination (e-THRIVE) images were acquired in the arterial phase after gadolinium ethoxybenzyl diethylenetriamine triamine pentaacetic acid (Gd-EOB-DTPA) administration. The region of interest (ROI) surrounding the HCC was copied to **c** and **d**. **b** Hepatobiliary phase of Gd-EOB-DTPA. **c** Diffusion-weighted imaging (DWI) with a b value of 800 s/mm². **d** Apparent diffusion coefficient (ADC) map with b values of 150 and 800 s/mm². **e** DWI with a b value of 800 s/mm² with dose map in

35GyE (green line). ROIs surrounding the irradiated and the normal liver were copied to **e** and **f**. **f** ADC map with b values of 150 and 800 s/mm² with dose map in 35GyE (green line). **g** In the arterial phase of Gd-EOB-DTPA at the first follow-up. The ROI surrounding the HCC was copied to **h** and **i**. **h** DWI with a b value of 800 s/mm² at the first follow-up. **i** ADC map with b values of 150 and 800 s/mm² at the first follow-up. **j** In the arterial phase of Gd-EOB-DTPA at the second follow-up. The ROI surrounding the HCC was copied to **k** and **l**. **k** DWI with a b value of 800 s/mm² at the second follow-up. **l** ADC map with b values of 150 and 800 s/mm² at the second follow-up

Table 2 ADC values, maximum tumor size, and tumor reduction ratio before and after ion beam therapy

	Baseline	First follow-up	Second follow-up
ADC of Tumor ($\times 10^{-3}$ mm ² /sec)	1.03 $\pm$ 0.17	1.42 $\pm$ 0.17	1.73 $\pm$ 0.16
	p<0.001		
	p<0.05		p<0.05
ADC of Irradiated liver ($\times 10^{-3}$ mm ² /sec)	0.93 $\pm$ 0.11	1.20 $\pm$ 0.08	1.36 $\pm$ 0.11
	p<0.05		p<0.05
ADC of Normal liver ($\times 10^{-3}$ mm ² /sec)	0.92 $\pm$ 0.09	0.94 $\pm$ 0.07	0.90 $\pm$ 0.08
	ns		ns
The maximum tumor size (mm)	24.55 $\pm$ 4.28	14.81 $\pm$ 7.12	10.77 $\pm$ 6.26
	p<0.001		p<0.001
Tumor reduction ratio (%)		64.43 $\pm$ 12.4	82.31 $\pm$ 8.74
		p<0.01	

ns not significant

$$\text{Reduction ratio} = 100 \times (D_{\text{pre}} - D_{\text{post}}) / D_{\text{pre}},$$

where D_{pre} is a multiplicative of the largest diameter of the tumor before ion therapy, and D_{post} is a multiplicative of the largest diameter of the tumor after ion therapy.

2.5 Follow-up

Patients were examined by Gd-EOB-DTPA MRI at 3 months (first follow-up) and 6 months (second follow-up) after ion beam therapy. The same MRI machine was used before and after the therapy.

2.6 Statistical Analysis

All statistical analyses were performed by use of GraphPad software (Prism version 5.02, San Diego, CA, USA). Two-sided tests were used, and $P < 0.05$ was considered to indicate statistical significance. The ADC values, as well as the maximum tumor sizes, before and after ion beam therapy were compared by use of the Friedman test. The

tumor reduction ratios before and after ion beam therapy were compared by use of the Wilcoxon t test.

The relationship among ADC values of the tumor, irradiated liver, normal liver, and each time point was compared by Kruskal–Wallis test. The relationship between the tumor reduction ratio at each follow-up and the ADC of the tumor values was assessed by linear regression analysis.

3 Results

The differences in ADC values among the various liver tissues are shown in Table 2. The ADC of the tumors was significantly higher after therapy than before therapy ($P < 0.001$). The ADC of the irradiated liver was also significantly higher after therapy than before therapy ($P = 0.007$). However, the ADC of the normal liver did not change in response to therapy ($P > 0.05$). The ADC of the tumor tended to be higher after therapy than before therapy. Moreover, the maximum tumor size tended to

Fig. 2 Relationship between apparent diffusion coefficient (ADC) values and various time points of liver after ion beam therapy. *ns* not significant

decrease after therapy when compared with the size before therapy ($P < 0.001$). The relationship between the tumor reduction ratio and the imaging time point is shown in Table 2. A strong correlation was found between the tumor reduction ratio and the imaging time point ($R = 0.73$, $P = 0.006$).

The relationship between the ADC values of each organ and any time point is shown in Fig. 2. The differences in ADC among the baseline groups were not statistically significant ($P > 0.05$), whereas those among the first follow-up groups were statistically significant ($P < 0.01$). There was a significant difference between the ADC of the tumor and the ADC of the normal liver at the first follow-up time point ($P < 0.01$). Further, there was a significant difference between the ADC of the normal liver and the ADC of the irradiated liver ($P < 0.05$). In addition, there was a significant difference between the ADC of the tumor and the ADC of the irradiated liver ($P < 0.05$).

The differences in ADC among the second follow-up groups were statistically significant ($P > 0.001$). There was a significant difference between the ADC of the tumor and that of the normal liver at the second follow-up ($P < 0.001$). Further, there was also a significant difference

between the ADC of the normal liver and that of the irradiated liver ($P < 0.01$), and there was a significant difference between the ADC of the tumor and that of the irradiated liver ($P < 0.05$).

In addition, there was no correlation between the tumor reduction ratio and the ADC of the tumor ($P > 0.05$), as shown in Fig. 3a, b. In all patients, the DCE-MRI after ion beam therapy showed tumor necrosis. The finding in a 60-year-old man with HCC of segment VII is illustrated in Fig. 4.

4 Discussion

In the present study, we evaluated the state of HCC after ion beam therapy by analyzing the ADC. Chen et al. measured the ADC value in HCC before and after TACE as a way of monitoring the response to treatment. They reported a significant increase in ADC values in HCC in response to TACE [15]. However, the ADC values were measured only for a short period of a few days after TACE. By contrast, in the present study we examined the ADC at longer time points after treatment.

In this study, the tumor ADC value increased significantly in response to treatment (Table 2). Malignant tumors have a high cell density. After treatment, tumor necrosis causes destruction of the cell membrane, and there is a resulting increase in water diffusion to the extracellular space. A decrease in the ADC value corresponds to a decrease in local diffusion, and an increase in the ADC value results in relaxation of limited diffusion, as observed in tumor cell death [22]. This result indicates that ion beam therapy results in necrosis and an increase in ADC values.

The ADC value of the irradiated liver had increased significantly by the time of the second follow-up (Table 2). In photon therapy, the liver threshold of photon exposure is defined as 30–35 Gy. However, even when the liver was irradiated with less than 35 Gy, the ADC values were reported to have increased significantly [16]. On the other hand, the ADC values at the time of the first follow-up were

Fig. 3 Relationship between tumor size reduction and ADC value at various time points. **a** First follow-up, and **b** second follow-up

Fig. 4 A 60-year-old man with hepatocellular carcinoma (HCC) of segment VII (arrows). **a** Ion beam therapy planning. **b** Diffusion-weighted imaging (DWI) with a b value of 800 s/mm² before ion beam therapy, **c** after ion beam therapy at the time of the first follow-up, and **d** after ion beam therapy at the time of the second follow-up. **e** ADC map with b values of 150 and 800 s/mm² before ion beam therapy. ADC value of tumor = 0.88×10^{-3} mm²/s, irradiated

liver = 0.92×10^{-3} mm²/s, normal liver = 0.89×10^{-3} mm²/s). **f** After ion beam therapy at the time of the first follow-up, ADC value of tumor = 1.26×10^{-3} mm²/s, irradiated liver = 1.15×10^{-3} mm²/s, normal liver = 0.89×10^{-3} mm²/s). **g** After ion beam therapy at the time of the second follow-up, ADC value of tumor = 1.68×10^{-3} mm²/s, irradiated liver = 1.28×10^{-3} mm²/s, normal liver = 0.85×10^{-3} mm²/s).

significantly different when we compared the irradiated liver and the normal liver, suggesting that the increases in ADC values were not necessarily consistent with the prescription dose for compared photon and ion beam. This fact suggests that the ADC values are different due to differences in the irradiation dose to the liver (Fig. 2).

Post-treatment DCE-MRI showed necrosis in all tumors. In highly vascular tissues, such as those in the liver, perfusion or blood flow cause significant signal decay when a low b value is used [23]. By contrast, a high b value almost completely excludes the effects of in vivo perfusion. Several previous studies utilized 0 and another b value, which makes it difficult to analyze the different components of ADC in detail [15, 16, 18–20, 22]. To avoid the effect of perfusion, we used b values of 150 and 800 in this study. The ADC in the irradiated liver is related to inflammation of the liver rather than to local elevation of blood flow to the liver. Moreover, the ADC values of the tumor and irradiated liver were increased at the time of the second follow-up. The tumor reduction ratio had increased significantly by the time of the second follow-up (Fig. 2), which is consistent with the current understanding that tumors decrease at a rapid pace until 6 months after ion beam therapy.

Generally, radiotherapy makes tumor necrosis or increase in extracellular space water diffusion, and increase in ADC value of the tumor [24]. We had speculated that the rate of tumor necrosis was related to the increased ADC values, but there was no correlation between the tumor reduction ratio and ADC values in our study (Fig. 3a, b). On the other hand, Koh et al. reported that there was a linear inverse correlation between the tumor reduction ratio and the ADC, and that the ADC increased significantly in the group of patients that responded to therapy [17]. However, Cui et al. reported that there was a weaker

correlation between the tumor reduction ratio and the pretreatment ADC [20]. These observations suggest that the ADC of the tumor differs depending on treatment. Moreover, tumor histology and efficacy of therapy may be useful in predicting the response to therapy.

The risk of inducing hepatic dysfunction should be considered when any therapy for HCC is utilized, especially in patients with chronic liver disease, such as cirrhosis or chronic hepatitis. Even when treatment is considered to have been successful, one must consider that HCC and intrahepatic metastasis are associated with the occurrence of chronic liver disease. Therefore, HCC treatments that are relatively noninvasive and that provide high local control are particularly beneficial. Although ion beam therapy appears to fulfill these criteria, it is often not a feasible option because most institutions currently do not have the facilities for this treatment modality.

Moreover, locally irradiated liver tissues have a diminished uptake of the Gd-EOB-DTPA in the liver parenchyma [25]. Although it is difficult to analyze the irradiated liver after the therapy, it can be evaluated in a non-invasive manner in tumors and in the liver by analysis of the ADC value.

This study has several limitations. First, the patient population was relatively small. Second, no pathologic evaluation was performed. Third, the ADC values were calculated by monoexponential analysis of the signal in this study, whereas bi-exponential analysis may have provided more detailed information regarding focal tissue non-invasively [26]. Fourth, recent studies have compared pretreatment of the ADC of the tumor with the tumor reduction ratio. It was discussed whether it was a predictive response to therapy or not. However, we compared the tumor reduction ratio to the after therapy of ADC of tumor

at each follow-up. In this study, all tumors showed a reduction in size after therapy, and the ADC of the tumor was significantly higher before than after therapy.

5 Conclusion

Inflammation of the liver occurs after treatment as a result of radiation doses from an ion beam, and the tumor reaches a state of necrosis. ADC value analysis provides a non-invasive assessment and yields focal information regarding the tumor and liver before and after ion beam therapy.

Acknowledgments We would like to thank Kei Katahira, Yuki Yamamoto, and Masaki Suga at the Department of Radiation Technology, Hyogo Ion Beam Medical Center, for their technological support.

Compliances with ethical standards

Conflict of interest I declare that I have no conflict of interest in connection with this paper.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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