学 術
Arts and Sciences
原 著

Clinical usefulness of the serial ADC analysis in follow-up evaluation after Gamma Knife surgery for metastatic brain tumors

転移性脳腫瘍に対するガンマナイフ治療後の継時的ADC解析の有用性

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【Abstract】

Magnetic resonance imaging (MRI) is usually carried out in follow-up evaluation after Gamma Knife surgery (GKS) for metastatic brain tumors. The purpose of this study is to assess the utility of serial measurements of the apparent diffusion coefficient (ADC) values in differentiating radiation effects from tumor recurrence. We enrolled 57 metastatic brain tumors (>10mm in maximum diameter) from 51 patients treated with GKS in our institution from February 2011 to September 2012. Diffusion weighted imaging was added to conventional MRI, and the ADC values were measured every three months at least. The ADC index was defined as the ratio of normalized minimum ADC value in the latest observation to that of the former observation and was used for chronological evaluation. During follow-up, four lesions were diagnosed as tumor recurrence. In these lesions, the ADC indices were lower than 1.00 when the tumors were diagnosed as recurrences. In the cases of good outcome, the ADC indices were higher than 1.00. Based on these results, a reduction of the ADC indices between two consecutive exams strongly suggests tumor recurrence. The serial ADC analysis can be one of the reasonable diagnostic tools to distinguish tumor recurrence from radiation necrosis in follow-up imaging after GKS.

【要旨】

転移性脳腫瘍に対するガンマナイフ治療（GKS）後の再発診断における，経時的なapparent diffusion coefficient（ADC）解析の有用性を検討した．51患者57病変を対象として病変部の最小ADC値を測定し，連続した二つの検査の比（ADC index）を求め，その変化を観察した．良好な経過をたどった症例ではADC indexは1.00以上の高値で推移したが，再発した4病変では診断時期に1.00以下に減少する傾向を示した．定量的指標であり，かつ簡便に求めることができるADC indexを用いた評価は，GKS後の再発と放射線壊死の鑑別において有用な手段であることが示唆された．

1 Introduction

In follow-up imaging after Gamma Knife surgery (GKS) for metastatic brain tumors, several examinations are performed in combination to discriminate between tumor recurrence and radiation necrosis [1-4]. Magnetic resonance imaging (MRI) is generally used for a morphological diagnosis. On the other hand, Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) provide functional imagings and these are useful for differentiation of tumor recurrences and adverse radiation effects [2-4]. However, radioisotope examinations such as SPECT and PET are not available at all of the facilities and cost much more than MRI. Hence, in order to diagnose tumor regrowth rationally, we utilized the Apparent Diffusion Coefficient (ADC) values, which were easily obtained by adding Diffusion Weighted Imaging (DWI) to conventional MRI protocol. Since MRI is simple, widely available and low cost tool compare to SPECT and PET, it can be taken as consecutive examination. Goldman M, et al. [5)] reported a useful prognostic measure of tumor response using the ADC values at the initial post-GKS follow-up. Their study, however, has a limitation that patients often underwent follow-up at off-site locations, and they could not standardize follow-up imaging protocols. In the present study, we defined a quantitative index of the ADC value (ADC in-

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dex) for follow-up evaluation after GKS and analyzed the ADC index chronologically.

2 Materials and methods

This study was approved by institutional review board (IRB) of our hospital (IRB No. 363). We took care not to infringe on the patients' right to privacy by making the data anonymous.

2-1 Patient characteristics

From February 2011 to September 2012, 57 metastatic brain tumors (>10mm in maximum diameter) from 51 patients were enrolled in the present study. Patients who underwent prior radiosurgery and craniotomy were excluded. We also excluded patients with MRI evidence of hemorrhagic metastases at pre-treatment. Patient characteristics, tumor location, and primary cancer are presented in Table. All patients were performed GKS using the Leksel Model C Gamma Knife (Elekta Instruments AB, Stockholm, Sweden), and underwent consecutive MRI examinations in our institution.

Table Patient characteristics

Characteristic	Value
Total no. of patients	51
Men/women	30/21
Age (years), median (range)	66 (33-89)
Tumor location	
Frontal	18
Temporal	6
Occipital	5
Parietal	10
Basal ganglia	3
Brain stem	5
Cerebellum	10
Primary cancer	
Lung	34
Breast	6
Rectum	3
Kidney	3
Esophagus	2
Others	3

2-2 Magnetic resonance imaging

We employed 1.5-tesla MRI system (Achieva; Philips Healthcare, Best, The Netherlands) with 8-channel head coil. Conventional MRI consisted of axial T2 weighted turbo spin echo, contrast-enhanced T1 weighed fast field echo, and coronal contrast-enhanced T1 weighted spin echo sequences.

DWI was performed in the axial plain using a single-shot spin echo, echo planar imaging sequence with the following parameters: repetition time = 1886msec, echo time = 68msec, matrix = 112 × 86, field of view = 230mm, slice thickness = 6mm, slice gap = 1.5mm, number of signals averaged = 1, b value = 0 and 1000sec/mm2, acquisition time = 23sec. The ADC map was computed from the raw DWI data by use of the standard scanner console software. In addition, contrast enhanced T1 weighted spin echo image which was same as DWI for a field of view, a slice thickness and a slice gap was acquired, in order to set the region of interest (ROI) on the ADC map (see section 2-3).

2-3 Serial ADC measurements

The ADC values of metastatic brain tumors were measured every three months at least. A radiological technologist (K. K) and a neurosurgeon (O. N) set the ROI for each lesion by consensus as follows. First, we compared contrast-enhanced T1 weighted image to T2 weighted image carefully, and drew the ROI in the tumor lesion on the contrast-enhanced T1 weighted image which was same as DWI for a field of view, a slice thickness and a slice gap. Next, the T1 weighted image with the ROI and the ADC map were displayed side by side, and the ROI was copied and pasted on the ADC map. The form of the ROI was modified as necessary. The minimum ADC values for each ROI were measured. The ADC value of tumor was normalized to normal-appearing white matter. The ADC index was determined as the ratio of normalized minimum ADC value in the latest observation to that of the former observation. In the present study, The ADC indices were calculated serially during the follow-up. The ADC index was regarded as 1.3 when drawing the ROI was difficult due to tumor shrinkage (i.e., successful therapeutic response) with reference to the previous report[5].

Lesions were diagnosed as tumor recurrence and closely observed when the following clinical signs were observed: an increase in tumor size in contrast-enhanced T1 weighted image, a hot spot in Thallium-201 chloride SPECT[2], and deterioration in neurological symptoms.

3 Results

3-1 Serial ADC measurements

Change of the ADC index in serial follow-up after GKS are shown in **Fig. 1**. Among 57 lesions, four cases were diagnosed as tumor recurrence and another two cases needed intensive follow-up. In the lesions that showed good response after treatment, the ADC indices were higher than 1.00. In contrast, the ADC indices were lower than 1.00 when tumor recurrence were suspected.

3-2 Case presentation

Case 1. This 72-year-old man had 37mm single brain metastasis in the left parietal lobe from lung cancer (**Fig. 2 a**). The lesion was treated by three-session GKS with 10Gy in the peripheral dose on each fraction[6]. The ADC index in this case showed typical decrease at the time of recurrence (**Fig. 2 g**). At the 2nd follow-up, the lesion was well-controlled and the ADC index increased (**Fig. 2 b**, **g**). At the 3rd imaging, the reduction in the ADC index associated with tumor regrowth was observed (**Fig.2 c**, **g**). The lesion was diagnosed as a recurrence and retreatment was performed. The ADC indices were high during next two examinations (**Fig.2 d**, **e**, **g**), but dropped down again at the 6th follow-up and then the second retreatment was needed (**Fig. 2 f, g**).

Case 2. This 76-year-old man had 22mm single brain metastasis in the right parietal lobe from lung cancer (**Fig. 3 a**). The lesion was ir-

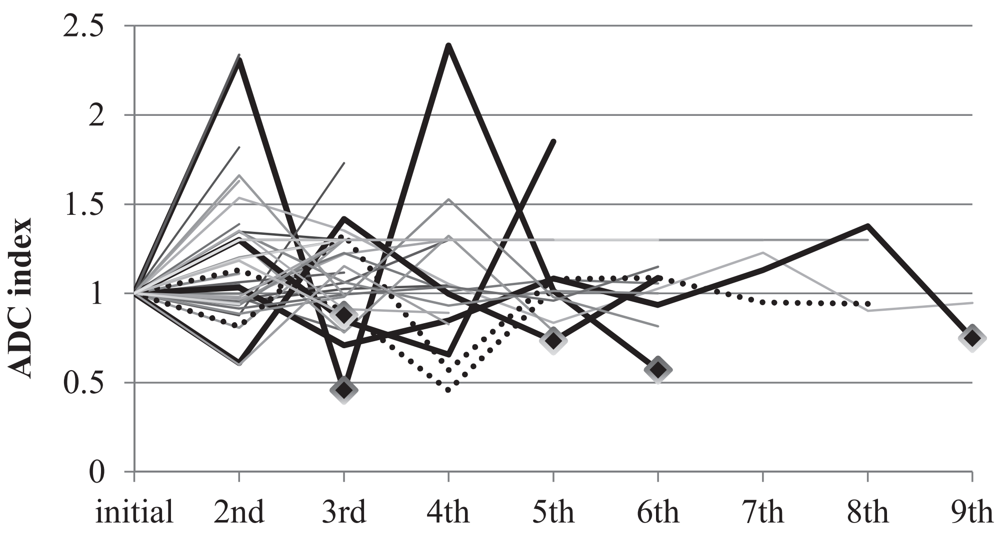

Fig. 1 Change of the ADC index in serial follow-up

Bold lines indicate retreatment cases, and *dashed lines* indicate intensive follow-up cases. The ADC indices were higher than 1.00 in the cases that followed good response after treatment, whereas the ADC indices were lower than 1.00 when we diagnosed tumor recurrence (*rhombuses*).

radiated with 22Gy in peripheral dose. At the 2nd follow-up, the ADC index decreased although there was no tumor regrowth (**Fig. 3 b**, **f**). As shown in MR images, the intratumoral bleeding occurred after irradiation in this case (**Fig. 3 b**). The ADC indices at the 3rd and 4th follow-up were higher than or equal to 1.00 (**Fig. 3 c**, **d**, **f**), but decreased again to 0.73 at the 5th follow-up (**Fig. 3 e**, **f**). The lesion was diagnosed as recurrence and retreated.

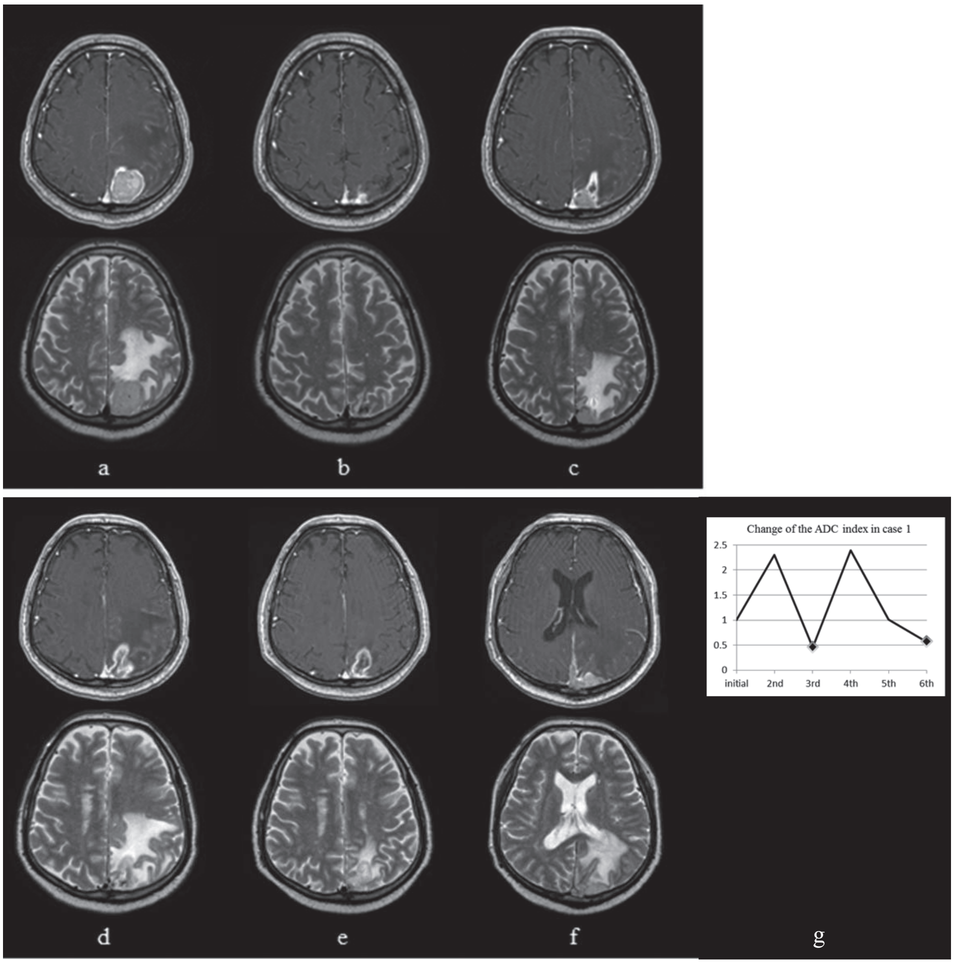

Fig. 2 Serial MRIs obtained in Case 1

a) Pre-GKS, these images demonstrate a metastatic brain tumor in the left parietal lobe.
b) 2nd follow-up, the lesion showed marked shrinkage and the peritumoral edema subsided. The ADC index was 2.31.
c) 3rd follow-up, the ADC index decreased to 0.46. The lesion was diagnosed as a recurrence and retreatment was performed.
d), e) 4th and 5th follow-up respectively, the ADC remained high value (2.39 at 4th and 1.02 at 5th follow-up).
f) 6th follow-up, the ADC index dropped down again (0.29), and the second retreatment was needed.
g) Temporal change in ADC index, the ADC indices decreased to lower than 1.00 when retreatments were needed (*rhombuses*).

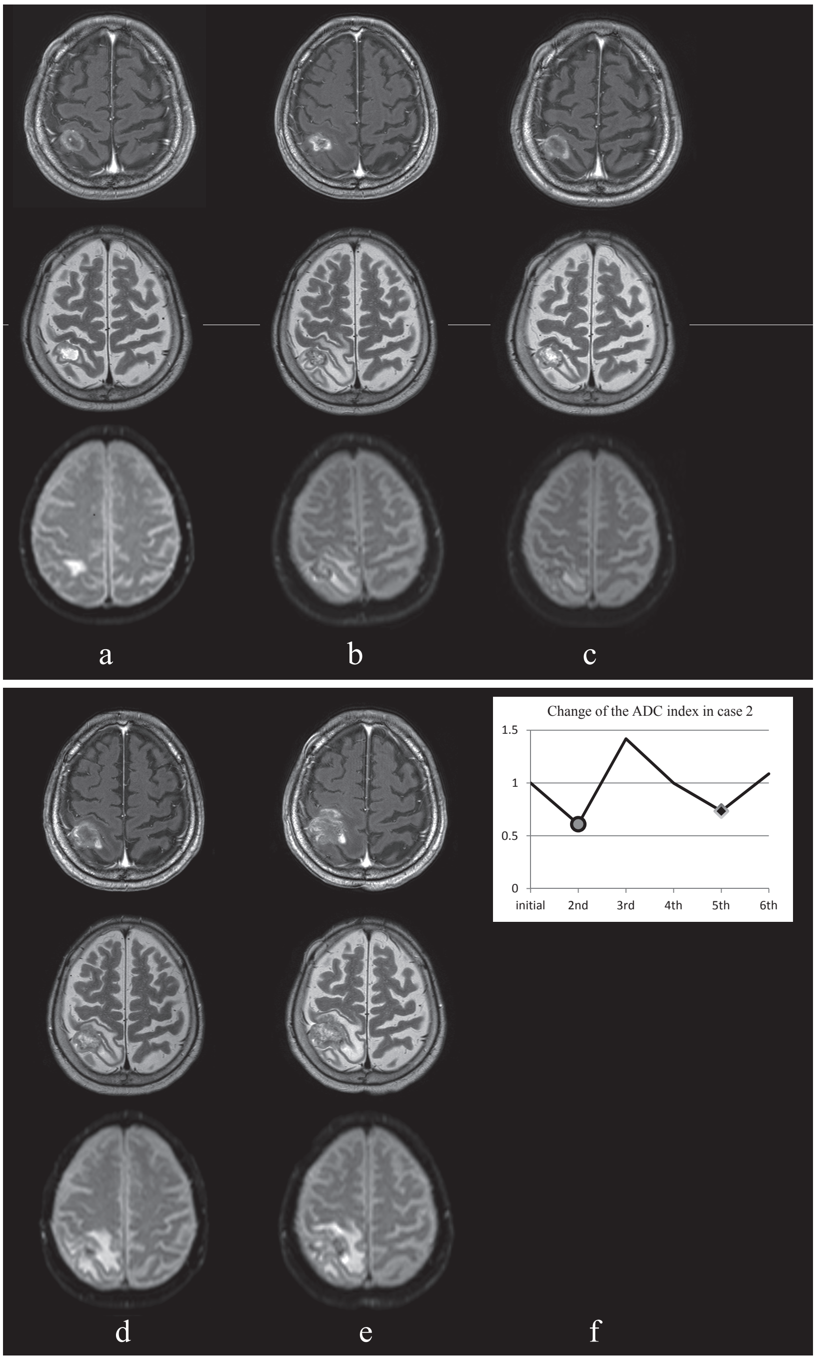

Fig. 3 Serial MRIs obtained in Case 2

a) Pre-GKS, these images depict brain metastasis in the right parietal lobe.
b) 2nd follow-up, the tumor size reduction was observed, but the ADC index decreased to 0.61. The intratumoral bleeding occurred after irradiation.
c) 3rd follow-up, the ADC index increased to 1.42.
d) 4th follow-up, the ADC index was 1.00.
e) 5th follow-up, the tumor increased in size, and the ADC index decreased to 0.73. The lesion was diagnosed as recurrence and treated again.
f) Temporal change in ADC index, note that the ADC index went down to lower than 1.00 when intratumoral bleeding was observed (*circle*). *Rhombus* represents recurrence.

4 Discussion

To differentiate tumor recurrence from adverse radiation effects after radiosurgery is significant clinical issue on patient practical management. Although functional imaging methods including SPECT and PET are useful, these are not routinely available. Meanwhile, the utility of the ADC value in differentiating between these conditions has been reported [5, 7]. Since the ADC value is easily measured by adding DWI to conventional MRI protocol, such an image analysis method is suitable for repeated examinations if it would provide reliable information. We defined the ADC index and observed its temporal change. The present study aims to assess the efficacy and limitations of the ADC index analysis after GKS for metastatic brain tumors.

The ADC value reflects the mobility of water in the tumor. The extracellular water increases in association with a decrease in the cellularity of tumor tissue, as tumor cells undergo necrosis or apoptosis due to irradiation [5, 7]. Because the ADC value is inversely correlated with cellularity, necrotic tissues and cystic lesions have high values [8]. In contrast, solid tumors and tumor regrowth indicate low ADC values. The data obtained in the present study were consistent with the finding of previous studies. The ADC indices were higher than 1.00 in the cases of good outcome and were lower than 1.00 when tumor recurrence were strongly suspected, suggesting that the reduction of the ADC value between two consecutive exams meant recurrence.

Our retreatment case 1 presented the typical change of the ADC index in serial follow-up evaluation after GKS. In the lesion consisting of a solid portion and a component of radiation necrosis, ADC index analysis is particularly effective method for accurate diagnosis of recurrent tumor. Our retreatment case 2 demonstrated that the ADC index decreased in spite of tumor shrinkage. Follow-up MR images revealed the intratumoral bleeding after GKS in this case. In no signal region on T2 weighted echo planar imaging, the signal is not detected on DWI with motion proving gradient owing to the susceptibility effect derived from hemoglobin in the hemorrhagic portion. Thus, the reduction of the ADC index might not suggest recurrence in the lesion with the intratumoral bleeding.

Huang CF, et al. [7] showed measurement of the ADC value could be used to evaluate the tumor response to GKS. This study, however, was limited to patients with solid or predominantly solid metastases, in contrast to the present study which include cystic, necrotic, and heterogeneous lesion as well. Thus, the ADC index can be applied to miscellaneous metastases in follow-up evaluation after GKS.

Kano et al. [1] reported a 'T1/T2 mismatch' method to differentiate tumor progression from radiation effects by use of T2 weighted image and contrast-enhanced T1 weighted image. Besides, Cha J, et al. [9] found that the presence of three-layer pattern of ADC was highly specific for radiation necrosis. The combined analysis of the ADC pattern with regional cerebral blood flow may have added value in the correct differentiation. The methods predicted a radiation induced effect with high sensitivity and specificity. By adding serial ADC follow-up to their methods, diagnostic accuracy may be further improved.

In Japan, The Ministry of Health, Labour and Welfare requires that radiological technologists should assist physicians in radiographic image interpretation. In this sense, the ADC index is suitable for an objective evaluation as it has a quantitative value. Therefore, serial ADC measurements could have potential to be an effective tool when radiological technologists advise physicians on diagnostic imaging to distinguish recurrent tumor from radiation necrosis.

The ADC index analysis has several limitations. First, tumor recurrence was defined only by MRI, Thallium-201 chloride SPECT, and deterioration in neurological symptoms without histologic confirmation. Second, the steroid therapy may slightly affect the ADC value [6]. We generally use steroid medications for patients with brain metastatic tumors to alleviate neurological symptoms by decreasing the peritumoral edema. It is necessary to take into account for the phenomenon in serial ADC measurements. Finally, the significant reduction of the ADC value is observed in the intratumoral bleeding after GKS, such as in our case 2. Even though the ADC index may be lower than 1.00 in this situation, it would be easy to differentiate hemorrhagic lesion from tumor recurrence when serially evaluated in conjunction with conventional MRI. Although the ADC index analysis has still limitations, it might be valuable tool supporting diagnosis of recurrence in the post GKS follow-up.

5 Conclusions

We report the useful method using DWI in follow-up imaging after GKS. The ADC indices were higher than 1.00 in the cases that followed good outcome after treatment. For the recurrent cases, the ADC indices were lower than 1.00. Serial analysis of the ADC index is a reasonable method to distinguish tumor recurrence from radiation necrosis in follow-up evaluation for metastatic brain tumors.

We presented this study in part at the 28th Japan Conference on Radiological Technologists held in Nagoya, Japan in September 2012, and received a letter of recommendation of the paper submission.

Conflict of interest

None.

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