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Contrast-enhanced fluid-attenuated inversion-recovery (FLAIR) versus contrast-enhanced T1 MRI in the evaluation of intracranial tumors: A comparative study

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ABSTRACT

INTRODUCTION: At most institutions, the favored contrast MR sequence is T1-weighted imaging (T1WI). However, lesion enhancement is occasionally inconspicuous on T1WI.
Objective: This study aims to evaluate the diagnostic value of contrast-enhanced FLAIR compared to contrast-enhanced T1WI for intracranial tumors and to offer data for further clinical judgment.
METHODS: 88 consecutive cases of intracranial tumors referred for contrast-enhanced brain MRI were analyzed. FLAIR and T1 were used alternately in equal percentages as the first contrast-enhanced sequence to avoid delayed contrast-enhancement effects of the lesions. Six quantitative criteria were considered: lesion-to-white matter contrast ratio (CR) and contrast-to-noise ratio (CNR), lesion-to-gray matter CR and CNR, and lesion-to-cerebrospinal fluid CR and CNR. For qualitative evaluation, two experienced radiologists assessed lesion conspicuity on contrast-enhanced-T1WI and FLAIR sequences using the following three scales: 1, FLAIR superior; 2, sequences equal; 3, T1 superior.
RESULTS: For quantitative measurement, the contrast enhanced-FLAIR lesion-to-white matter, lesion-to-cerebrospinal fluid CR, and CNR values were statistically superior to those of the contrast enhanced-T1 weighted images ($p = 0.001$ in all). However, lesion-to-gray matter CR and CNR were slightly higher on CE-FLAIR, but with no statistically significant difference ($p = 0.159, 0.184$, respectively). For qualitative evaluation, both radiologists assessed that contrast enhanced-FLAIR images were superior to contrast enhanced-T1 weighted images for the evaluation of lesion conspicuity, especially when it was performed as the second sequence.
CONCLUSION: FLAIR sequence was superior or comparable to T1 sequence, especially when performed as a second post-contrast sequence. Using contrast enhanced-FLAIR as a routine MRI sequence will increase diagnostic confidence.

Keywords: Intracranial Tumors, MRI, Comparative Study, Enhanced Contrast.

INTRODUCTION

Intravenous contrast material is frequently used to evaluate various pathological conditions of the brain during MRI and to improve the conspicuity of small lesions [1]. Gadolinium-chelates conventional

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contrast-enhanced T1-weighted spin-echo MRI (CE-T1WI) are the primary sequences used to obtain post-contrast T1-weighted images [2]. Pre and post-contrast T1-spin echo (T1-SE) scans are usually compared for assessing the various characteristics of lesions such as vascularity, internal necrosis, or a breach in the blood-brain barrier. Post-contrast T1SE scans utilize the T1-shortening effect of gadolinium for conspicuous delineation of a variety of lesions. In addition to T1-shortening, gadolinium also produces a T2-shortening effect which is inversely proportional to gadolinium concentration, resulting in increased contrast to noise ratio [2-4].

Although CE-T1W images are useful in making a diagnosis of location and qualification for intracranial tumors and can help improve ability in evaluating treatment effect and follow up, this method has certain limitations in diagnosis, e.g., it cannot effectively detect lesions in the lateral ventricle or cortical areas.

Recent reports, however, have revealed the ability of postcontrast fluid-attenuated inversion recovery (FLAIR) MR images to visualize contrast enhancement of brain lesions. FLAIR is a special inversion recovery pulse sequence with a long repetition time (TR) and echo time (TE) and an inversion time (TI) that effectively nulls signals from the cerebrospinal fluid (CSF) [5-7]. The mild T1 effect of the FLAIR sequence that is produced by the long TI is responsible for contrast enhancement on these heavily T2W images [8]; thus, lesions that show enhancement on CE-T1WI also show enhancement on contrast-enhanced FLAIR (CE-FLAIR) images. The post-gadolinium enhancement seen on T2-FLAIR images is due to the T2- prolongation effect of various lesions and T1-shortening effect of gadolinium acting in synergism [9].

The purpose of this study was to compare CE-T1WI and CE-FLAIR images in depicting intracranial tumors and to provide more information for clinical diagnosis and the potential value of clinical applications of CE-FLAIR sequence in diagnosing these tumors.

METHODS

Study design

This study was undertaken between the period of August 2019 and October 2021. A total of 88 patients undergoing contrast-enhanced MR imaging for approved or supposed brain tumors were screened and enrolled consecutively in this prospective comparative study.

This study was conducted under the Declaration of Helsinki and was approved by the hospital's ethics and scientific research committee (Ref. code: 122/2019). Informed consent was gained from all the patients involved in the study, and their personal health information was safeguarded.

Data collection

Seventy-three patients had primary tumors and 15 patients had metastatic tumors from the remote sites. The primary tumors consisted mainly of meningiomas (n=31), glioma (n=26), and pituitary adenoma (n=6). Less frequent primary tumors such as lymphoma, hemangioblastoma, and neurocytoma (n=10) were also included in this study. The primary neoplasms of the metastatic tumors were lung cancer (n=4), breast cancer (n=3), rectal cancer (n=2), ovarian cancer (n=2) and unknown primary (n=4), respectively. Diagnoses were made based on biopsy results (n=5) or clinical and radiologic findings (n=83). Among the 15 patients with metastatic tumors, eight had multiple tumors. In cases of multiple tumors in a patient, only the largest one of them was selected and evaluated.

Magnetic resonance imaging (MRI) was performed on 3 T (Philips Medical Systems, Best, The Netherlands). A controlled imaging protocol comprising of T1-weighted spin-echo (T1SE), T2- weighted fast SE, FLAIR acquisitions before contrast injection, and T1SE and FLAIR acquisitions (axial planes) after injection ensured protocol uniformity within individual patients.

The parameters for the T1-SE sequence were as follows: TR, 400 ms; TE, 9 ms; section thickness, 5 mm; intersection gap, 1 mm; FOV, 23 cm; acquisition matrix, 168 x 144, and acquisition time: 1 min 02 seconds.

The imaging parameters of contrast-enhanced FLAIR imaging were TR: 6000 ms, TE: 82 ms, TI: 2500 ms, FOV: 25 cm, image matrix: 210× 256, slice thickness: 5 mm, slice interval: 1 mm, and acquisition time: 2 minutes.

Post-contrast imaging was commenced one minute following intravenous injection of dimegluminegadopentetate (Magnevist; 0.1 mmol/kg of body weight; Bayer Pharma AG, Germany).

T1-SE and FLAIR were used alternately as the first CE sequence to avoid delayed contrast enhancement effects of the lesions and subsequent bias. Therefore, in the first 44 patients who were imaged, T1SE was the first CE sequence while in the remaining 44 patients, FLAIR was the first CE sequence.

The images were then subjected to meticulous evaluation by two expert radiologists.

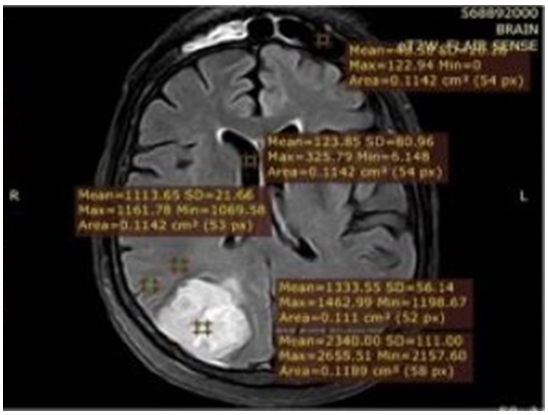

Figure 1: *An example of ROIs placing. A 67 years old woman with a right occipital meningioma on CE-FLAIR MRI. ROI 1 was placed in the tumor parenchyma. ROI 2 was placed in the peritumoral cortical grey matter area. ROI 3 was placed in the peritumoral white matter area. ROI 4 was placed in a homogenous area of CSF in the lateral ventricle. ROI 5 was placed in the air space of the frontal sinus to measure the image noise.*

All images from each patient were evaluated in a global matched pairs fashion. Images were presented for review on a multi-monitor imaging workstation. For each randomized patient number, all images from the native examination were displayed simultaneously with the corresponding images from the post-contrast examination. Each radiologist as a reader was able to perform all routine interactive image-manipulation functions (e.g., window/level, zoom, pan) on both image sets. If the post-injection images from either sequence were considered technically inadequate by any of the readers (e.g., if artifacts compromised interpretability), no further assessment was performed for that patient by that reader.

Quantitative evaluation

Region-of-interest (ROI) analysis was performed for CE-T1SE and CE-FLAIR images by a single investigator. The size of the ROIs was similar to each other (0.11cm2). For quantitative assessment, signal intensities (SIs) were measured by an ROI analysis of the tumor, WM, cortical GM, and cerebrospinal fluid (CSF), respectively. Signal intensity was also measured in the airspace for the measurement of image noise. The signal intensity of the tumor was measured within a homogeneously enhancing solid portion. The gray and WM SIs were calculated in normal-appearing areas neighboring the tumor, which showed no edema or atrophy. The CSF SI was measured in a homogeneous region within the lateral ventricles. Figure 1 shows an example of ROI placing. Six quantitative criteria were considered: lesion-to-WM contrast ratio (CR) and contrast-to-noise ratio (CNR), lesion-to-GM CR and CNR, and lesion-to-CSF CR and CNR. The difference between the lesion and WM SIs divided by the WM SI was considered as the lesion to-WM CR [CR lesion-to WM = (SI lesion – SIWM) / SIWM] while the difference between the signals from the lesion and WM divided by the standard deviation (SD) of measured image noise was considered as the lesion-to-WM CNR [CNR lesion-to WM = (SI lesion – SI WM) / SD background noise]. Similar calculations were performed for lesion-to-GM CR and CNR, and lesion-to-CSF CR and CNR.

Contrast enhancement rates (CER) were evaluated by pre-and post-contrast FLAIR and T1W images as the following:

CER= [SI post – SI pre) / SI pre] x 100 %.

Qualitative evaluation

Two independent radiologists evaluated all images, who were unaffiliated with the study centers and blinded to all patient clinical and radiologic information, as well as all interpretations by on-site investigators. These images were technically adequate and were evaluated qualitatively for diagnostic information and scored in terms of the following: 1) lesion border delineation, 2) definition of disease extent, 3) visualization of lesion internal morphology and 4) lesion contrast enhancement compared with surrounding normal tissue. Simultaneously, each one of the radiologists separately evaluated precontrast and postcontrast FLAIR and T1W imaging. Three scales were used to grade the lesion conspicuity: 1, CE-FLAIR superior; 2, sequences equal; 3, CE-T1 superior.

Statistical analysis

Collected data was inputted into an excel sheet (Microsoft excel sheet 16) and loaded into Statistical Package for Social Sciences (SPSS), SPSS® for Windows, Version 24.0 (IBM Corp, Armonk, NY). Descriptive statistics were presented

Table 1: Quantitative values of CRs, and CNRs for CE-FLAIR and CE-T1 sequences

	Lesion-WM CR	Lesion-GM CR	Lesion-CSF CR	Lesion-WM CNR	Lesion-GM CNR	Lesion-CSF CNR
CE-FLAIR	1.08± 0.61	0.74± 0.51	24.68± 12.94	42.90 ±3.79	35.11 ±33.68	77.38 ±45.25
CE-T1	0.54± 0.34	0.65± 0.42	2.69 ±1.16	27.10 ±2.46	29.75 ±24.55	55.29 ±32.67
r	-0.032	0.052	0.225	0.097	0.201	0.347
p value	0.001	0.159	0.001	0.001	0.184	0.001

Note- values represent the mean± standard deviation. CR: contrast ratio; CNR: contrast-to-noise ratio; WM: white matter; GM: gray matter; CSF: cerebrospinal fluid; FLAIR: fluid-attenuated inversion recovery; r: correlation coefficient

through frequency distribution tables and graphs. Continuous variables were articulated as mean ± SD. A paired sample t-test was used to analyze the continuous variables and find out the significance of the difference between means of readings of the lesion by different sequences (T1 and FLAIR). The Kappa agreement test was used to find out the degree and significance of the agreement between two senior radiologists to decide which sequence was better. A P-value at 0.05 was considered as a cut-off point for discrimination of significance of differences or agreement.

RESULTS

The range of ages for this group was 12 – 87 years, with a mean age of 48.56±18.28. Out of 88 intracranial tumors, 52.3% of these lesions were seen in females (n= 46) and 47.7% in males (n=42)

In evaluating the degree of contrast enhancement among the total 88 cases, CE-FLAIR showed significantly lesser enhancement compared to CE-T1WI (42.04 ±26.89 versus 55.02 ±40.83, r= 0.292, P= 0.005).

The quantitative evaluation results of lesion-to-WM, lesion-to GM, and lesion-to-CSF CRs and CNRs are summarized in Table 1. The FLAIR lesion-to-WM CR and CNR, lesion-to-CSF CR and CNR values were higher than those of the CE-T1 images and they showed statistically significant differences (P= 0.001 in all). However, The FLAIR lesion-to-GM CR and CNR values were higher than those of the CE-T1 images, however, they showed no statistically significant differences (P= 0.159, 0.184, respectively).

Table 2 shows the qualitative comparison of lesion conspicuity between CE-FLAIR and CE-T1WI. Both radiologists agreed, with a moderate level of significance, in 45.5% of the total cases that the CE-FLAIR sequence was superior, while they agree in 28.4% that the CE-T1 sequence was superior (Kappa agreement value=0.671, P = 0.001).
Figures 2 and 3 were examples of these study cases where CE-FLAIR was used as the first and second post-contrast sequence respectively.

DISCUSSION

Gadolinium is the most commonly used intravenous contrast agent for imaging the brain. It aids in lesion discovery and improved categorization. Gadolinium causes the shortening of both T1 and T2 of the tissues in which it has accumulated. Due to the T1 shortening, there is contrast enhancement of a lesion on clinical MR images [10].
Conventional contrast-enhanced T1-weighted spin-echo MRI (short time of TR and TE) plays a critical role in the diagnosis of intracranial tumors. After intravenous administration of GD-DTPA, the

Table 2: Cross-tabulation showed the agreement level of two radiologists of total sample irrespective of which sequence is the first

			R2			
			1.0	2.0	3.0	Total
R1	1.0	Count	40	6	2	48
		% of Total	45.5%	6.8%	2.3%	54.5%
	2.0	Count	5	6	2	13
		% of Total	5.7%	6.8%	2.3%	14.8%
	3.0	Count	2	0	25	27
		% of Total	2.3%	0.0%	28.4%	30.7%
Total		Count	47	12	29	88
		% of Total	53.4%	13.6%	33.0%	100.0%

Kappa agreement value=0.671, p value= 0.001(moderate significant level of agreement); R1: the first radiologist, R2: the second radiologist; 1: CE-FLAIR is superior, 2: equal, 3: CE-T1 is superior.

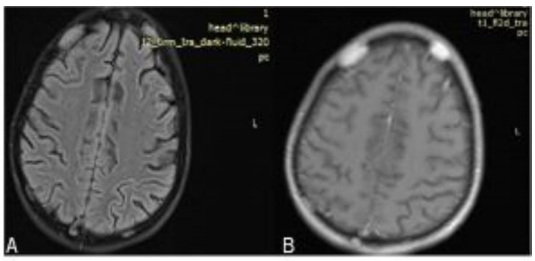

Figure 2: *A 30-year-old woman with meningeal metastases. CE-FLAIR (A) and CE-T1 (B) images show two enhancing lesions in the frontal region. The lesions enhancement and conspicuity are superior on T1 image than on FLAIR image. In this patient, FLAIR was performed as the first post-contrast sequence.*

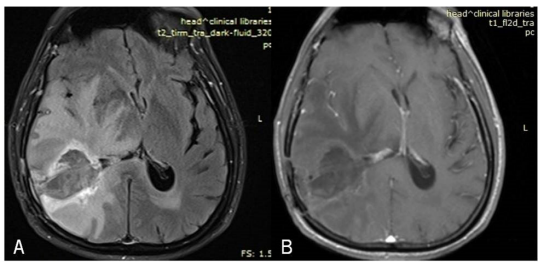

Figure 3: *CE-FLAIR (A) shows more ring enhancement in a patient with high-grade glioma (GBM) compared to that on the CE-T1 image (B). In this patient, FLAIR was performed as the second post-contrast sequence.*

contrast medium undergoes a dispersion into the body tissues that results in high signal intensity of the relevant tissues due to aggrandizement of the contrast disparity between the lesions and normal tissues [2,3]. This occurs due to the shortening of the time of T1 and T2 which takes relative priority of shortening the time of T1, which is termed contrast enhancement [2,3].

FLAIR images correspond to T2WI except for dark CSF which is attributed to the T1 effect present due to the long TI. After administration of gadolinium, there is T1 shortening which is seen as hyperintensity on FLAIR images; therefore, lesions showing enhancement on postcontrast T1WI will also enhance on postcontrast FLAIR images [11,12].

A FLAIR sequence that produces heavily T2-weighted and CSF nulled MR images are obtained by applying a lengthy time of TR and TE: 2000 ms of time of inversion (TI). FLAIR sequence has lower GWC but a much higher lesion-to-background signal ratio compared to T2WI, resulting in originally indistinct lesions proximal to the CSF to be apparent against a background of attenuated CSF [13,14]. Previously it was thought that the injection of gadolinium would not provide additional information [14]. However, several researchers [15,16,17] reported that the injection of gadolinium can intensify T1 effect on FLAIR images and that CE- FLAIR images can better detect superficial lesions compared to CE-T1WI. This was in disagreement with other studies [18,19].

FLAIR must be applied pre-and post- contrast administration to overcome the confusion arising from the hyperintensity detected when the FLAIR sequence is done only after gadolinium administration as this hyperintensity can be due to either T2 lengthening or T1 shortening. Ercan et al [10] showed that post-contrast FLAIR images are better in comparison to post-contrast T1WI in detecting the number of metastatic intracranial lesions, its conspicuity, and enhancement probably due to delayed enhancement in such lesions.

In this study regarding the evaluation of the degree of the contrast enhancement, CER of CE-T1WI was significantly stronger statistically than

that of CE-FLAIR sequence. This could be due to the following two reasons: (1) Because of rather longer TR, CE-FLAIR sequence has less T1 weight, i.e. light T1 relaxation effects exhibiting an increase of signal intensity in comparison to CE-T1WI. (2) Most tumor lesions exhibit hyperintensity on pre-contrast FLAIR images which lower the signal intensity difference between pre- and post-contrast FLAIR images to some extent. In this study, obvious contrast enhancement could be discerned in 80 cases (91.8%) by the naked eye, and the other 8 cases (8.2%) also exhibited enhancement after calculating the signal intensity pre and post-contrast administration. That is to say, CE-FLAIR sequence can demonstrate contrast enhancement of intracranial tumors and has a better clinical utility.

The results of this study regarding quantitative and qualitative analyses showed that CE-FLAIR sequence had superior lesion-to-WM, lesion-to-GM, lesion-to-CSF CR, and lesion conspicuity compared to CE-T1W images. There have been some reports [20,21] that showed different results to those of this study. This discrepancy might be caused by differences in types of diseases included in their investigations, as well as by differences in scanning parameters. Most of the previous investigations which showed different results to those of this study evaluated only the parenchymal lesions of the brain. However, in this study, 40 lesions (45.5%) were extra-axial tumors.

This study has some limitations. Firstly, various kinds of tumors were included in the study. The enhancement of brain tumors depends on various factors. They include histologic type, tumor vascularity, and preservation or breakdown of the blood-brain barrier. The lesion-to-background contrast of the brain tumors on T1-weighted image is also influenced by various factors, which are enhancement degree, size, and locations of the tumors and presence and absence of surrounding brain edema. Further studies confined to a specific type of tumor are needed. Secondly, in cases of multiple metastatic tumors, only the largest tumor was evaluated and it could result as a selection bias.

CONCLUSION

Contrast enhanced-FLAIR sequence is a valuable adjunct to CE-T1W imaging in equivocal cases of intracranial tumors, especially if it is performed as the second sequence. The addition of CE-FLAIR in the brain MRI protocol of intracranial tumors can increase diagnostic confidence and improve patient care..

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