Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/19446
DOI URL:http://dx.doi.org/10.21474/IJAR01/19446

RESEARCH ARTICLE

UTILITY OF CONTRAST-ENHANCED T2-FLAIR FOR IMAGING OF BRAIN METASTASESUSING A HALF-DOSE HIGH-RELAXIVITY CONTRAST AGENT IN COMPARISON WITH ROUTINE DOSE CONTRAST-ENHANCED BRAIN IMAGING

Dr. D. Thejesh[1], Prof. Dr. Debakumar Chakrabartty[2] and Dr. MD Imdadul Islam[3]

1. Postgraduate Resident, Dept of Radiology, Silchar Medical College, Assam.
2. Professor and HOD, Dept of Radiology, Silchar Medical College, Assam.
3. Assistant Professor, Dept of Radiology, Silchar Medical College, Assam.

Manuscript Info

Manuscript History
Received: 10 July 2024
Final Accepted: 14 August 2024
Published: September 2024

Key words: -
Half-Dose High Relaxivity Contrast Agent, Contrast-Enhanced Flair, Cost Saving Measure, Missed Lesions

Abstract

Aim & Objectives: This study aims to assess the efficacy of delayed contrast-enhanced T2 fluid-attenuated inversion recovery (CE-T2 FLAIR) by using half dose high relaxivity contrast agent to assess the degree of enhancement among the lesions and to detect additional metastatic brain lesions usually smaller lesions(<5mm), which are significantly missed on routine-dose CE-T1 weighted imaging (CE-T1WI).

Material & Methods: The main source of data for this study was radiologically diagnosed lung cancer patients who were clinically suspected to have brain metastasis referred from various departments of Silchar Medical College and Hospital. The studywas carried out for a period of 1 year from March 1, 2023, to February 29, 2024, A total of 40 patients with brain metastases were scanned using a SIEMENS TIM AVANTO 1.5T scanner, routine MR pulse sequences pre- and post-contrast administration were acquired.

Results: Out of 40 patients, males were more affected (57.5 %) than females (42.5 %). The highest number of cases were found between the 61-70 years age group with the lung (31 cases) being the most common primary malignancy causing brain metastases. A total of 90 lesions were detected among 40 patients which were grouped into A (25 lesions), B (36 lesions), and C (29 lesions) groups. A total of 6 lesions were missed on Routine dose contrast-enhanced brain imaging of which 2 lesions belong to group B (Rim enhancing lesions >5mm) and 4 lesions belong to group C (Lesions <5mm), however, these lesions were picked up on delayed half dose contrast-enhanced FLAIR images. The contrast ratio (CR) on 3 consecutive half dose CE-T2 FLAIR ranged between 59.09%-76.80%, suggesting that delay in imaging post-contrast administration resulted in a significant increase in the contrast ratio (CR) among metastatic lesions.

Conclusions: CE-T1-weighted sequences and CE-T2 FLAIR sequences complement each other effectively in evaluating brain metastases. Bigger and homogenously enhancing lesions are best seen on CE-T1-weighted sequences. Smaller lesions and lesions showing rim enhancement are best visualized on delayed (5 min) CE-T2 fluid-

Corresponding Author:- Prof. Dr. Debakumar Chakrabartty
Address:- Professor and HOD, Dept of Radiology, Silchar Medical College, Assam.

attenuated inversion recovery (FLAIR) sequences with half the dose ofcontrast agent (gadobenatedimeglumine) compared to routine dose CE-T1-weighted sequences. This approach serves as a cost-saving measure for both patients and the healthcare system.

……

Introduction:-

Brain metastases are the most common intra-axial brain tumour occurring in cancer patients which accounts for 40% of adult brain tumours and as per literature 25% of patients with a known primary malignancy develop metastasis eventually in their life[(1)], Among all the malignancies lung cancer is the most common malignancy that causes brain metastasis(19.9%)[(2)].

Magnetic resonance imaging (MRI) of the brain with and without contrast enhancement is the most common method for the detection of brain metastasis and also for tracking the progression of lesions[(3)] or to assess the efficacy of initiated therapy for treatment[(4)]

Gadolinium is the major component of the contrast used for MRI examination in patients suspected of brain metastasis, with contrast administration the clarity of the lesion and the detection of the lesion can be significantly improved, a higher dose of gadolinium-based contrast agents(GBCA) used better is the lesion characterization[(5)]. Among T2 weighted sequences, fluid-attenuated inversion recovery (FLAIR) is an inversion recovery sequence which picks up gadolinium in the tissue at low concentrations[(6)].The inherent property of FLAIR to null the cerebrospinal fluid (CSF) signal and intravascular signal[(7)] It helps detect various other brain pathologies after contrast administration. The post-contrast FLAIR is an excellent sequence especially to assess the involvement of meninges in conditions like meningoencephalitis and leptomeningeal carcinomatosis[(8)].

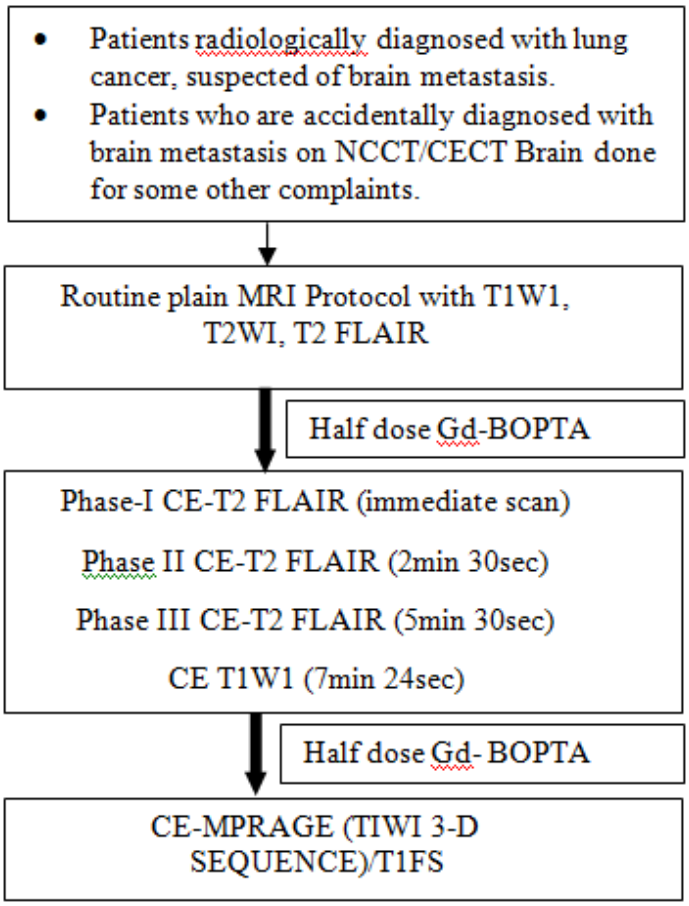
Earlier many studies were conducted which mostly focused on the use of Contrast-enhanced-T2 FLAIR(CE-T2 FLAIR) after administering the routine dose of GBCA; however, only a **few studies assessed the usage of low-dose CE-FLAIR for the detection of brain neoplasms including metastases and various other pathologies involving central nervous system(CNS)[(9)]**. Another important consideration to be assessed is the delay in contrast administration, as a higher delay post contrast administration when combined with CE-T2 FLAIR for image acquisition resulted in the accurate diagnosis of central nervous system (CNS) pathologies[(10)], which establishes a relationship with scanning time.

Materials and Methods:-

The present study was carried out in the Department of the Radiology, Silchar Medical College and Hospital, Silchar for a period of one year from 01-03- 2023 to 29-02-2024. The hospital is located in the Cachar district of Barak Valley in the state of Assam, India. It is the tertiary and referral centre for patients of different districts of the Barak Valley region of Assam and the nearby northeastern states of India.

Clinical MR imaging protocol

A total of 40 patients with brain metastases were scanned using a **SIEMENS TIM AVANTO 1.5T MR scanner**, and routine MR pulse sequences pre- and post-contrast administration were acquired.



Flowchart showing the method of imaging among study population

MR imaging analysis
The MR imaging data were evaluated and analyzed on a workstation (SIEMENS).

Lesion Grouping: The enhancement pattern of brain metastases was assessed and classified into solid- and ring-enhancing lesions. The longest diameter of the lesion was measured on both axial CE-MpRAGE/T1FS and axial CE-T2 FLAIR Sequences. The lesions were grouped according to their size (max diameter < or > 5 mm), and the enhancement pattern (solid or rim enhancement) was divided into the following groups:

- Group A: solid-enhancing lesions with >5mm diameter
- Group B: ring-enhancing lesions with >5mm diameter
- Group C: lesions with <5mm diameter.

Subjective Scoring of Enhancement Degree.
The degree of enhancement on CE-T2 FLAIR, CE-T1WI, and CE- MpRAGE/T1FS was qualitatively assessed using a 3-point scale by two examiners (Radiology Resident and Assistant Professor Department of Radiology, Silchar Medical College and hospital Silchar, Assam). The scoring criteria were as follows-**1 point: Poor enhancement** (the signal intensity of the lesions was almost equal to that of the adjacent white matter and hardly identifiable; missed lesions were also included in this group); **2 points: Moderate enhancement** (the signal intensity was moderately higher than that of the adjacent white matter, but reliably identifiable); and **3 points: Good enhancement** (the signal intensity was significantly higher than that of the adjacent white matter and easily identifiable).

Quantitative Index Measurement:
Calculation of contrast ratio (CR): is calculated for the 3 subsequent half-dose CE-T2 FLAIR sequences by using the formulae:

$CR = [(SI_{CE\text{-}T2FLAIR} - SI_{NWM})/SI_{NWM}] \times 100\%$.

- $SI_{CE\text{-}T2FLAIR}$ represents the signal intensity of the lesion after enhancement
- SI_{NWM} represents the signal intensity of the region of interest (ROI) based on normal-appearing white matter (NWM) adjacent to the tumour.

ROI Placements:
Both the examiners drew the ROIs (Region of interest) independently. A function tool was utilized to fuse all sequences, including non-enhance FLAIR, three consecutive sequences of CE-T2 FLAIR, Half dose CE-T1WI, and Routine dose CE-MpRAGE/T1FS Sequences. ROIs were initially drawn on CE-T2 FLAIR images and then propagated across all other sequences to ensure consistent positioning. If the ROIs did not align in different sequences after propagation, the ROIs were independently redrawn to maintain the same position as accurately as possible. An ROI was drawn to encompass the entire lesion and was placed within a homogeneously enhanced area if the lesion showed enhancement. For ring-enhancing lesions, the ROI was placed on a uniformly appearing part of the ring, avoiding hemorrhagic, necrotic, and vascular areas.

Statistical analysis:
Data entered in MS Excel sheet and SPSS version 28.0 was used for statistical analysis. The measured data were presented as mean [SD]. CR values of 3 successive CE-T2 FLAIR sequences from all the metastatic lesions were compared among A, B, and C groups using a paired t-test for CR values. The chi-square test was used to compare the qualitative degree of enhancement among the 3 sequences and $P<0.05$ was considered statistically significant for all the assessed parameters.

Results and Observations:-

Out of 40 patients, males were more affected (57.5 %) as compared to females (42.5 %). The highest number of cases were found between the 61-70 years age group with the lung (31 cases) being the most common primary malignancy causing brain metastases. A total of 90 lesions were detected among 40 patients which were grouped into A (25 lesions), B (36 lesions), and C (29 lesions) groups.

The **Contrast Ratio (CR)** measured across three subsequent half-dose CE-T2FLAIR sequences were as follows CR_{phase1}= 59.09% (SD:30.06), CR_{phase2}=66.43% (SD:36.3), CR_{phase3}=76.80% (SD:37.18). CR_{phase1} was significantly lower than CR_{phase2} ($P<0.003$), and CR_{phase2} was significantly lower than CR_{phase3} ($P<0.021$), Thus indicating that increasing the scan acquisition time after contrast administration led to a significant increase in the contrast ratio in brain metastasis.

Group A: The degree of enhancement on half-dose CE-T2 FLAIR was higher than, half-dose CE-T1WI ($P<0.01$) and routine-dose CE-T1WI ($P=0.039$). however, no significant appreciable difference was found between half-dose CE-T1WI and routine-dose CE-T1 weighted imaging ($P=0.046$) sequences.

Table1:- Group A, Comparison of the enhancement degree of three sequences of solid enhancing lesions with diameters of > 5mm.

	Half dose CE-T2 FLAIR	**Half dose CE-T1WI**	**Routine dose CE-T1FS/MpRAGE**
Three points	25	23	25
Two points	0	2	0
One point	0	0	0
Total	25	25	25

Group B: The degree of enhancement of lesions on half-dose CE-T2 FLAIR was higher than half-dose CE-T1WI ($P<0.01$) however,no significant difference was found with routine dose CE-T1WI($P=0.13$). On comparing between half-dose CE-T1WI and routine-dose CE-T1WI/ MpRAGE, no significant difference was appreciated ($P=0.046$).

Table 2: - Group B, Comparison of the enhancement degree of three sequences of ring-enhancing lesions with diameters of > 5mm. (^{M}= number of missed lesions).

	Half dose CE-T2 FLAIR	**Half dose CE-T1WI**	**Routine dose CE-T1FS/MpRAGE**
Three points	36	30	32

Two points	0	2	2
One point	0	4(2^{M})	2(2^{M})
Total	36	36	36

Group C: The degree of enhancement of lesions was significantly higher on half-dose CE-T2 FLAIR compared to both half-dose CE-T1WI ($P < 0.01$) and routine-dose CE-T1WI ($P < 0.01$). Additionally, the degree of enhancement on routine-dose CE-T1WI was greater than on half-dose CE-T1WI ($P = 0.001$).

Table 3:- Group C, Comparison of the enhancement degree of three sequences of lesions with diameters of < 5mm. (^{M}= number of missed lesions).

	Half dose CE-T2 FLAIR	**Half dose CE-T1WI**	**Routine dose CE-T1FS/MpRAGE**
Three points	26	10	15
Two points	3	11	10
One point	0	8(8^{M})	4(4^{M})
Total	29	29	29

Discussion:-

Most of the patients with brain metastasis present with a single lesion. For these patients, detecting metastases is crucial for determining the appropriate treatment. Small metastases, often less than 5 mm in size, typically lack vasogenic edema and exhibit only slight enhancement. As a result, they are frequently missed on non-enhanced T2 FLAIR or enhanced T1-weighted sequences[(1)].

The growth of the metastatic lesions is very fast and, at the time of presentation itself, the lesions are very big and are associated with changes like significant edema and leptomeningeal spread. Since the lesions in early stages are significantly small in diameter and are generally not associated with secondary changes or mass effects, they are generally missed[(1)], however, these small lesions respond to the therapies hence it is of utmost importance to detect these lesions at early stages to enhance the chances of favourable outcomesfor patients[(11)]. Larger lesions are commonly associated with secondary changes pose significant challenges in deciding treatment protocols and are associated with bad prognosis[(12)].Possible explanations for poor response to the treatment protocols in larger lesions could be reduced intracranial penetration of various modes of therapies, and the number of metastatic lesions at the time of diagnosis.More invasive procedures like neurosurgical resections and the use of toxic chemotherapeutic and radiation therapies are reserved for advanced and multifocal disease[(13)]. Hence it is of utmost importance to detect the lesions in their early stages for planning effective treatment protocols.

Scanning time significantly influences the signal intensity of lesions, as the infiltration of gadolinium from blood vessels into the extracellular space is a dynamic process. Delaying imaging can enhance signal intensity by allowing more prolonged perfusion of the contrast agent through the leaky neovasculature within metastases[(14)].Delayed CE-T2 FLAIR in meningeal diseases could provide more accurate information compared to delayed CE-T1WI or early CE-T2 FLAIR[(15)].

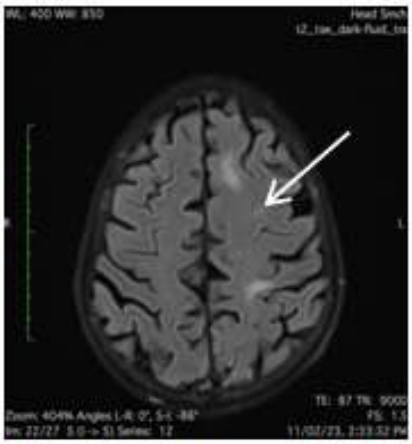
In our study, we conducted three consecutive phases of CE-T2 FLAIR to evaluate the effect of scanning time on T2 FLAIR. We observed that later time points (2 minutes 31 seconds to 5 minutes 30 seconds) during CE-T2 FLAIR acquisitions exhibited a higher degree of enhancement compared to the initial acquisition. This implies that a delay of at least 3–5 minutes is recommended for postcontrast CE-T2 FLAIR imaging.

In our study, we observed that half-dose CE-T2 FLAIR provided a better degree of enhancement and a higher detection rate for small metastases compared to CE-T1WI or CE-MpRAGE. It is observed in a few previous studies that only one-quarter of the routine dose of gadolinium is required for CE-T2 FLAIR to attain a signal enhancement equivalent to that of CE-T1WI. This phenomenon can be attributed to the unique T1-weighting of the T2 FLAIR sequence. The mild T1-weighting induced by the long inversion time (TI) combined with the T1-shortening effects of gadolinium makes the T2 FLAIR sequence more sensitive to low concentrations of contrast agents than conventional contrast-enhanced T1 sequences[(6)(16)].

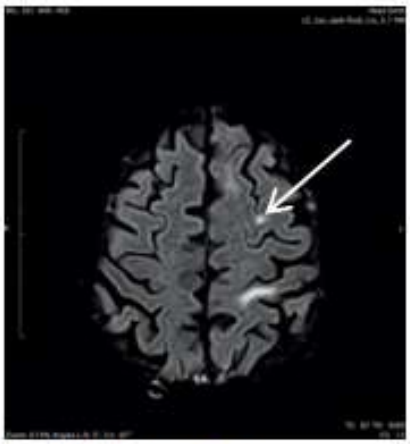
The peripheral margin of an invasive tumour tends to have lower vascular permeability[(17)], which enhances the

sensitivity ofCE-T2 FLAIR in delineating the boundaries of brain metastases[18].

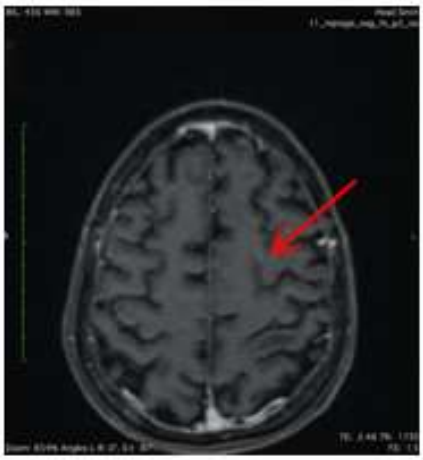
Using high-dose contrast on CE-T1WI can increase the detection rate of metastases[19], it also results in an increased risk of adverse effects in cancer patients. Using half-dose CE-T2 FLAIR not only reduces the amount of contrast agent needed but also enhances the detection rate of small cerebral metastases[9]. The hyperintensity of the lesion on non-enhanced FLAIR due to prolonged T2 weighting might obscure the true enhancement of the lesion on post-contrast sequence hence use of post-contrast FLAIR is limited in neuroimaging. Hence complementing post-contrast FLAIR with post-contrast T1WI will improve the exact delineation of the lesion margin and also in the detection of additional lesions.



Unenhanced T2-FLAIR



B) Half dose CE-FLAIR(5.4min)



C) Full dose T1WI

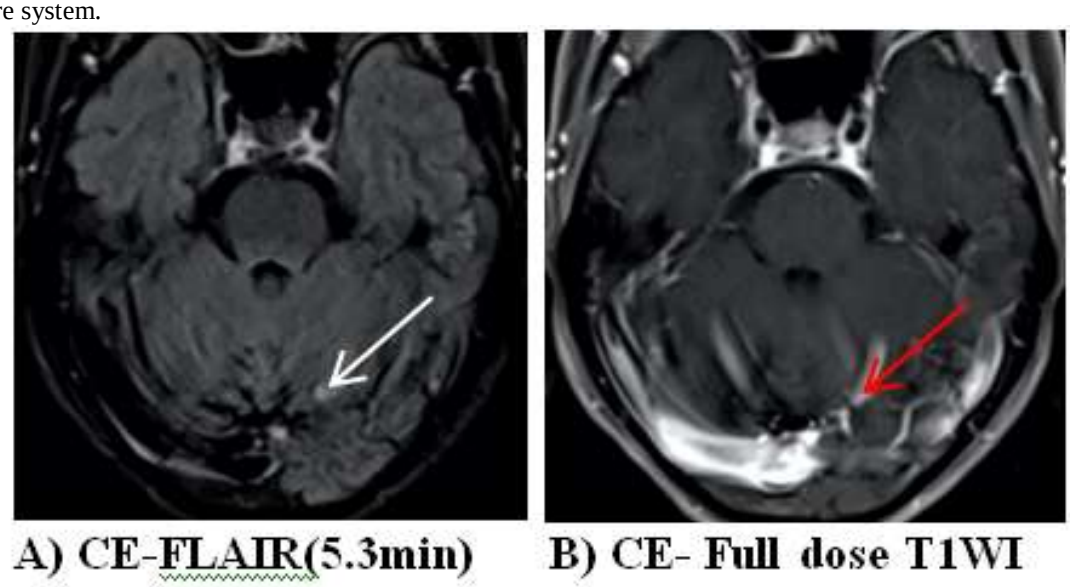
Case1: Ill-defined hyperintensity was noted in the left middle frontal gyrus on NE-FLAIR (Fig A), which was noted enhancing on CE-FLAIR(5.4min) (Fig B). This lesion was missed (Red Arrow) on full dose CE-T1WI (Fig C).

Limitations

First, the sample size in each group is relatively small, which may negatively affect the statistical results. Second, while it would have been beneficial to study the signal enhancement of brain metastases on half-dose CE-T2 FLAIR images over a longer time period, this was not feasible for ethical reasons. Patients with cancer and brain metastases are typically limited in the amount of time they can undergo MR imaging, restricting the duration of the examination.

Conclusions:-

CE-T1-weighted sequences and CE-T2 FLAIR sequences complement each other effectively in evaluating brain metastases. Bigger and homogenously enhancing lesions are best seen on CE-T1-weighted sequences,smaller lesions and lesions showing rim enhancement are best visualized on delayed (5 min) **CE-T2 fluid-attenuated inversion recovery (FLAIR)** sequences with **half the dose of contrast agent** (gadobenatedimeglumine) compared to routine dose CE-T1-weighted sequences. This approach serves as a cost-saving measure for both patients and the healthcare system.



Case 2: Homogenously enhancing lesion (Group C) was noted in the left cerebellar hemisphere on half dose CE-T2 FLAIR (Fig A), which was missed (Red Arrow) on full dose CE-T1WI (Fig B) due to the presence of vessels.

References:-

1. Essig M, Knopp MV, Schoenberg SO, Hawighorst H, Wenz F, Debus J, et al. Cerebral Gliomas and Metastases: Assessment with Contrast-enhanced Fast Fluid-attenuated Inversion-Recovery MR Imaging. Radiology. 1999 Feb;210(2):551–7.
2. Aizer AA, Lee EQ. Brain Metastases. Neurologic Clinics. 2018 Aug;36(3):557–77.
3. Park J, Kim EY. Contrast-enhanced, three-dimensional, whole-brain, black-blood imaging: Application to small brain metastases: CE Whole-Brain Black-Blood Imagin g. Magn Reson Med. 2010 Mar;63(3):553–61.
4. Fahlström M, Fransson S, Blomquist E, Nyholm T, Larsson EM. Dynamic contrast-enhanced magnetic resonance imaging may act as a biomarker for vascular damage in normal appearing brain tissue after radiotherapy in patients with glioblastoma. Acta Radiologica Open. 2018 Nov;7(11):205846011880881.
5. Mathews VP, King JC, Elster AD, Hamilton CA. Cerebral infarction: effects of dose and magnetization transfer saturation at gadolinium-enhanced MR imaging. Radiology. 1994 Feb;190(2):547–52.
6. Mathews VP, Caldemeyer KS, Lowe MJ, Greenspan SL, Weber DM, Ulmer JL. Brain: Gadolinium-enhanced Fast Fluid-attenuated Inversion-Recovery MR Imaging. Radiology. 1999 Apr;211(1):257–63.
7. Terae S, Yoshida D, Kudo K, Tha KK, Fujino M, Miyasaka K. Contrast-enhanced FLAIR imaging in combination with pre- and postcontrast magnetization transfer T1-weighted imaging: Usefulness in the evaluation of brain metastases. Magnetic Resonance Imaging. 2007 Mar;25(3):479–87.
8. Rumpel H, Chan LL. Serial FLAIR Imaging After Gd-DTPA Contrast: Pitfalls in Stroke Trial Magnetic Resonance Imaging. Stroke. 2003 Mar;34(3):797–8.
9. 9. Jin T, Ge M, Huang R, Yang Y, Liu T, Zhan Q, et al. Utility of Contrast-Enhanced T2 FLAIR for Imaging Brain Metastases Using a Half-dose High-Relaxivity Contrast Agent. AJNR Am J Neuroradiol. 2021 Mar;42(3):457–63.
10. Kremer S, Abu Eid M, Bierry G, Bogorin A, Koob M, Dietemann JL, et al. Accuracy of delayed post-contrast flair MR imaging for the diagnosis of leptomeningeal infectious or tumoral diseases. Journal of Neuroradiology. 2006 Dec;33(5):285–91.

11. Ahn SJ, Chung TS, Chang JH, Lee SK. The Added Value of Double Dose Gadolinium Enhanced 3D T2 Fluid-Attenuated Inversion Recovery for Evaluating Small Brain Metastases. Yonsei Med J. 2014;55(5):1231.
12. Chang EL, Hassenbusch SJ, Shiu AS, Lang FF, Allen PK, Sawaya R, et al. The Role of Tumor Size in the Radiosurgical Management of Patients with Ambiguous Brain Metastases. Neurosurgery. 2003 Aug;53(2):272–81.
13. Cagney DN, Martin AM, Catalano PJ, Brown PD, Alexander BM, Lin NU, et al. Implications of Screening for Brain Metastases in Patients With Breast Cancer and Non–Small Cell Lung Cancer. JAMA Oncol. 2018 Jul 1;4(7):1001.
14. Lüdemann L, Grieger W, Wurm R, Wust P, Zimmer C. Quantitative measurement of leakage volume and permeability in gliomas, meningiomas and brain metastases with dynamic contrast-enhanced MRI. Magnetic Resonance Imaging. 2005 Oct;23(8):833–41.
15. Kremer S, Abu Eid M, Bierry G, Bogorin A, Koob M, Dietemann JL, et al. Accuracy of delayed post-contrast flair MR imaging for the diagnosis of leptomeningeal infectious or tumoral diseases. Journal of Neuroradiology. 2006 Dec;33(5):285–91.
16. Jackson EF, Hayman LA. Meningeal Enhancement on Fast FLAIR Images. Radiology. 2000 Jun;215(3):922–4.
17. Hasegawa H, Ushio Y, Hayakawa T, Yamada K, Mogami H. Changes of the blood-brain barrier in experimental metastatic brain tumors. Journal of Neurosurgery. 1983 Aug;59(2):304–10.
18. Ercan N, Gultekin S, Celik H, Tali TE, Oner YA, Erbas G. Diagnostic value of contrast-enhanced fluid-attenuated inversion recovery mr imaging of intracranial metastases. AJNR Am J Neuroradiol. 2004 May;25(5):761–5.
19. Akeson P, Larsson EM, Kristoffersen DT, Jonsson E, Holtås S. Brain metastases--comparison of gadodiamide injection-enhanced MR imaging at standard and high dose, contrast-enhanced CT and non-contrast-enhanced MR imaging. Acta Radiol. 1995 May;36(3):300–6.