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Discrimination between glioblastoma and solitary brain metastasis: a quantitative analysis based on FLAIR signal intensity

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Abstract. – OBJECTIVE: This study determined the diagnostic performance of fluid-attenuated inversion recovery (FLAIR) signal intensity (SI) in discriminating between glioblastoma (GBM) and solitary brain metastasis (SBM).

PATIENTS AND METHODS: We recruited 40 patients with a histologically confirmed diagnosis of GBM or SBM who underwent conventional 3 Tesla magnetic resonance imaging before surgery or biopsy between August 2020 and January 2022. Three regions of interest were placed to assess FLAIR SI: the enhancing region (eFLAIR), the peritumoral region (pFLAIR), and the contralateral normal white matter (nFLAIR). The diagnostic performance of significantly different parameters between the two tumor entities was analyzed by receiver operating characteristic (ROC) curve analysis.

RESULTS: The pFLAIR SI was significantly lower in GBM than in SBM ($p < 0.05$). The eFLAIR SI and the SI ratio eFLAIR and nFLAIR (e/nFLAIR) were significantly higher in GBM than in SBM ($p < 0.05$). On ROC curve analysis, the e/nFLAIR ratio provided the highest area under the curve value of 81%, with a sensitivity of 80.8% and a specificity of 85.7%, for distinguishing between the two tumor types.

CONCLUSIONS: The eFLAIR, pFLAIR, and e/nFLAIR parameters are useful for differentiating between GBM and SBM.

Key Words:
FLAIR, Glioblastoma, Solitary brain metastasis, Quantitative measurement.

Introduction

Glioblastoma (GBM) and brain metastasis that develop from tumors in other origins are the most common malignant intracranial tumors detected in adults[1]. Although brain metastasis is typically suspected in the context of multiple lesions or known primary malignancy, distinguishing between GBM and solitary brain metastases (SBM) in the absence of other known lesions can be challenging, due to these two tumor types having similar imaging features on conventional magnetic resonance imaging (MRI)[2]. The extracranial metastasis of GBM is rare and generally does not require systemic screening, whereas an SBM without a pre-existing medical history requires a thorough systemic examination to determine the type and location of the primary tumor. Therefore, obtaining a correct diagnosis of GBM or SBM plays a crucial role in treatment planning and prognosis[3,4].

The peritumoral regions of both GBM and SBM demonstrate hyperintensity on fluid-attenuated inversion recovery (FLAIR). GBM typically shows infiltrating characteristics in the surrounding tissue, whereas SBM does not have this feature[5,6]. Therefore, distinguishing between peritumoral edema and peritumoral infiltration is key to discriminating between GBM and SBM[7]. Previous studies[8-11] have examined the use of advanced imaging sequences, such as spectroscopy, perfusion, diffusion, and diffusion tensor imaging, for the assessment of the peritumoral region. However, the results of these studies remain controversial[5,8,12,13], and these advanced techniques may not be available in some MR machines, requiring additional time, advanced processes, and higher costs.

The vasogenic edema region of SBM is hypothesized to contain a larger volume of extracellular water than the infiltrate region of GBM[2,8]. Thus, the peritumoral region of GBM may have a lower signal intensity (SI) on FLAIR than the peritumoral region of SBM. To our knowledge, few studies[14,15] have applied

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Table I. Pulse sequences used on conventional magnetic resonance imaging.

Parameters / Sequences	TR (msec)	TE (msec)	Slice thickness (mm)	Slide space (mm)	FOV	Matrix
T1SE	2325	25	5	1	240	320 × 224
FLAIR	8500	117	5	1.5	240	320 × 200
T2 GE	440	10	5	1	240	320 × 160
DWI	5202	78	5	1	240	116 × 116
T1 GE 3D contrast	7	3	1.2	1	230	320 × 224

TR: repetition time; TE: echo time; FOV: field of view; T1SE: T1-weighted spin-echo; FLAIR: fluid-attenuated inversion recovery; GE: gradient-echo; DWI: diffusion-weighted imaging; 3D: 3-dimensional.

quantitative analysis to conventional MRI techniques for the differential diagnosis between these two entities. In this study, we assessed the ability of FLAIR SI to differentiate between GBM and SBM.

Patients and Methods

Study Population

This retrospective study included 40 patients with GBM or SBM that were histopathologically confirmed following surgery or biopsy at Viet Duc Hospital, Hanoi, Vietnam, between August 2020 and January 2022. All patients underwent conventional preoperative MRI, and all presented with a solitary intracranial tumor. Ethical clearance was received from the institutional ethics committee of Hanoi Medical University (Ref: 2682/QD-ĐHYHN), and the requirement for informed consent from patients was waived.

MRI Technique

All MRI examinations were conducted on 3 Tesla MRI GE SIGNA Pioneer (GE Healthcare, Chicago, IL, USA), using a head coil with conventional and diffusion sequences, including axial or sagittal T1-weighted (T1W), FLAIR, axial T2 gradient-echo, and axial diffusion-weighted imaging (DWI) with apparent diffusion coefficient map reconstruction (Table I). The contrast agent was gadolinium-diethylene triamine pentaacetic acid, which was administered intravenously using a 0.1-0.2 ml/kg body weight dose, followed by 3-plane T1 imaging reconstruction.

Imaging Analysis

Two radiologists with over 10 years of neuroradiology experience who were blinded to the histopathological results analyzed the patients' images on the software system INFINITT PACS (INFINITT Healthcare, South Korea). Disagreements were handled by discussion.

Three regions of interest (ROIs, covering 15-30 mm^2) were placed on the enhancing region, the peritumoral region, and the contralateral normal white matter region of axial FLAIR images. The same regions were used in both pre-and post-contrast T1 images from each patient. The enhancing region of the tumor was defined on post-contrast T1 images, which were synchronized with the FLAIR images. The peritumoral region was defined as the region that appears hyperintense on FLAIR, hypointense on pre-contrast T1 imaging, and without enhancement on post-contrast T1 imaging. The contralateral normal white matter was defined as the region that displays normal SI on FLAIR and pre-contrast T1 images and no enhancement on post-contrast T1 imaging in the contralateral hemisphere in the same slice as the lesion. Bleeding (hyperintense on T1, hypointense on T2), calcification (hypointense on all pulse sequences), cystic regions (hypointense on T1, hyperintense on FLAIR, no enhancement), and blood vessels were avoided when selecting ROIs. The relative FLAIR SI ratios between the enhancing region and the contralateral white matter and between the peritumoral region and the contralateral normal white matter were also calculated (Figures 1 and 2).

Statistical Analysis

Statistical data were analyzed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used for non-normally distributed variables, and Student's *t*-test was used for normally distributed variables to assess the differences between the GBM and SBM groups. A p-value < 0.05 was considered significant. The receiver operating characteristic (ROC) curve was analyzed for variables identified as significantly different between the two tumors to determine effective cutoff points. The areas under the ROC

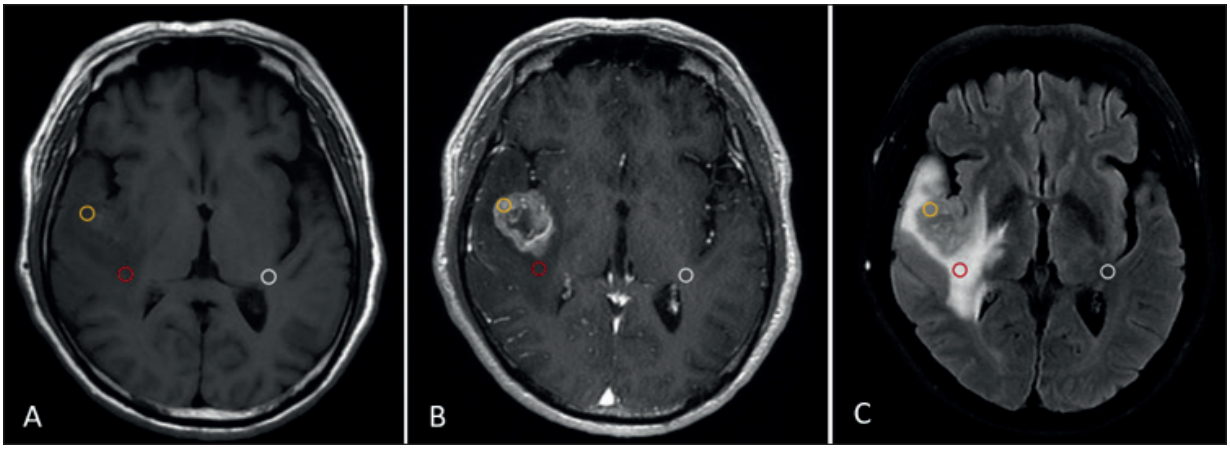

Figure 1. A 64-year-old male patient with a right temporal glioblastoma. Pre-contrast axial T1-weighted image (**A**), post-contrast axial T1-weighted image (**B**), and fluid-attenuated inversion recovery (FLAIR) (**C**) show a heterogeneous mass with central necrosis, ring enhancement, and surrounding infiltration and edema. Three regions of interest (ROIs) were obtained in the enhancing region (yellow ROI), the peritumoral region (red ROI), and the contralateral normal white matter (white ROI).

curve (AUC), sensitivity (Se), specificity (Sp), negative predictive value (NPV), and positive predictive value (PPV) for the differential diagnosis between the two tumor groups were calculated.

Results

Patients Characteristics

A total of 40 patients, including 26 diagnosed with GBM and 14 diagnosed with SBM (12 patients with metastases from lung cancer, 2 patients with metastases of unknown origin) were enrolled. There were more men than women (24 and 16, respectively) and the mean ages of patients diagnosed with GBM and SBM were 59.04 ± 12.09 years (range: 19 to 81 years) and 58.79 ± 6.14 years (range: 50 to 71 years), respectively. No significant difference in mean age was identified between the two tumor types ($p > 0.05$).

The Application of FLAIR SI for the Differential Diagnosis Between GBM and SBM

The mean FLAIR SI value in the enhancing region (eFLAIR) of GBM (820.19 ± 86.39) was

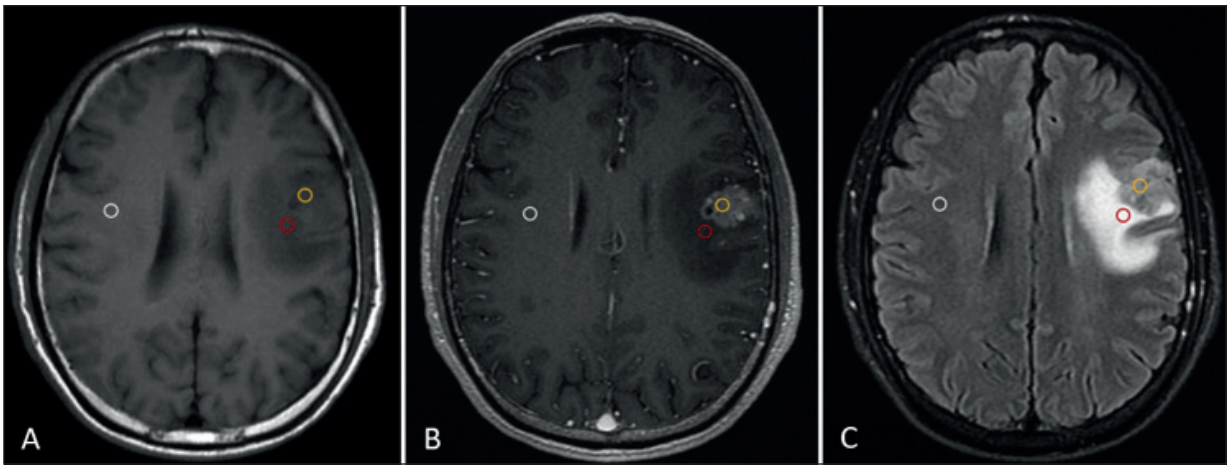

Figure 2. A 56-year-old male patient with left frontal lobe solitary brain metastasis due to lung cancer. Pre-contrast axial T1-weighted image (**A**), post-contrast axial T1-weighted image (**B**), and fluid-attenuated inversion recovery (FLAIR) (**C**) show a heterogeneous mass with ring enhancement and surrounding vasogenic edema. Three regions of interest (ROIs) were obtained in the enhanced solid tumor region (yellow ROI), the peritumoral edema region (red ROI), the contralateral normal white matter (white ROI).

Table II. FLAIR SI values in enhancing region, peritumoral region, and contralateral normal white matter in patients with GBM and SBM.

Parameters	GBM	SBM	p
eFLAIR	820.19 ± 86.39	735.06 ± 114.92	**0.012***
pFLAIR	969.37 ± 111.34	1068.67 ± 137.03	**0.031***
nFLAIR	471.11 ± 50.05	506.11 ± 76.59	0.089

FLAIR: fluid-attenuated inversion recovery; SI: signal intensity; e: enhancing region of the tumor; p: the peritumoral region; n: contralateral normal white matter; GBM: glioblastoma; SBM: solitary brain metastasis
* Significant difference ($p < 0.05$) using Student's *t*-test.

significantly higher than that of SBM (735.06 ± 114.92; Table II). The mean FLAIR SI value in the peritumoral region (pFLAIR) of GBM (969.37 ± 111.34) was significantly lower than that of SBM (1068.67 ± 137.03; Table II). The FLAIR SI ratio between the enhancing region and the contralateral normal white matter (e/nFLAIR) of GBM (1.76 ± 0.26) was significantly higher than in that of SBM (1.47 ± 0.23; Table III). The FLAIR SI ratios between the peritumoral region and the contralateral normal white matter (p/nFLAIR) were not significantly different between GBM and SBM.

The AUC for eFLAIR was 0.75 (Figure 3), and a cutoff value of 808.11 allowed for the differential diagnosis between these two entities with a Se of 65.4% and a Sp of 78.6% (Table IV). The AUC for pFLAIR was 0.71 (Figure 4), and a cutoff value of 1039.96 allowed for the differential diagnosis between these two entities with a Se of 71.4% and a Sp of 80.8% (Table IV). The AUC was for e/nFLAIR was 0.81 (Figure 3), and a cutoff value of 1.63 allowed for the differential diagnosis between these two entities with a Se of 80.8% and a Sp of 85.7% (Table IV).

Table III. The FLAIR SI ratios of the enhancing region and the peritumoral region relative to the contralateral normal white matter.

Parameters	GBM	SBM	p
e/nFLAIR	1.76 ± 0.26	1.47 ± 0.23	**0.001***
p/nFLAIR	2.08 ± 0.29	2.13 ± 0.25	0.542

FLAIR: fluid-attenuated inversion recovery; SI: signal intensity; e: enhancing region of the tumor; p: the peritumoral region; n: contralateral normal white matter; GBM: glioblastoma; SBM: solitary brain metastasis.
*Significant difference ($p < 0.05$) using Student's *t*-test.

Discussion

FLAIR is an available sequence on all MR systems and is regularly used in brain tumor examinations[16]. In general, GBM is presented as a heterogeneous mass with a necrotic center and irregular contrast enhancement, whereas SBM is presented as a more intensely enhancing mass with clearer margins. However, these features are not specific and can be found in both types of tumors[2,16]. Several qualitative studies[16-18] have attempted to use the FLAIR sequence to differentiate between these two tumor types. Tang et al[17] hypothesized that SBM consisted of lesions located in the subcortical white matter and gray-white matter junctions, associated with a large degree of vasogenic edema in the surrounding white matter. Therefore, the detection of adjacent cortical regions that are unaffected by vasogenic edema but display an abnormal signal without enhancement suggests the presence of glioma cell infiltrates. The study by Tang et al[17] showed that cortical signal abnormalities that were tumor-adjacent but unenhanced, following the injection of contrast agent, could be detected in 16 of 36 gliomas, but in only 3 of 34 brain metastases, thus resulting in a high Sp of 91% and a low Se of 44% for distinguishing between these two types of tumors. Maurer et al[15] conducted a quantitative study that measured the size of the enhancing tumor, the thickness of the enhancing region on post-contrast T1W, and the size of the peritumoral edema on FLAIR. This research showed that the ratio between the maximum diameter of the peritumor edema and the maximum diameter of the enhancing mass was significantly lower for GBM than for SBM, with a cutoff value of 2.35, resulting in a Se of 84% and a Sp of 45%. Tumors may be located in different locations within the brain parenchyma, such as the gray matter, subcortical white matter, or deep white matter, which would influence the FLAIR SI. In our study, we identified no significant differences in nFLAIR values between the two groups ($p > 0.05$). Therefore, we normalized the SI values by calculating the ratios of the SI values within the enhancing area of the tumor and the peritumoral edema relative to the SI values of the opposite normal white matter to minimize inaccuracies.

Peritumoral edema in GBM and SBM occurs due to different mechanisms, although they both represent vasogenic edema[10]. The peritumoral SBM edema consists of normal brain parenchyma featuring purely vasogenic edema caused by

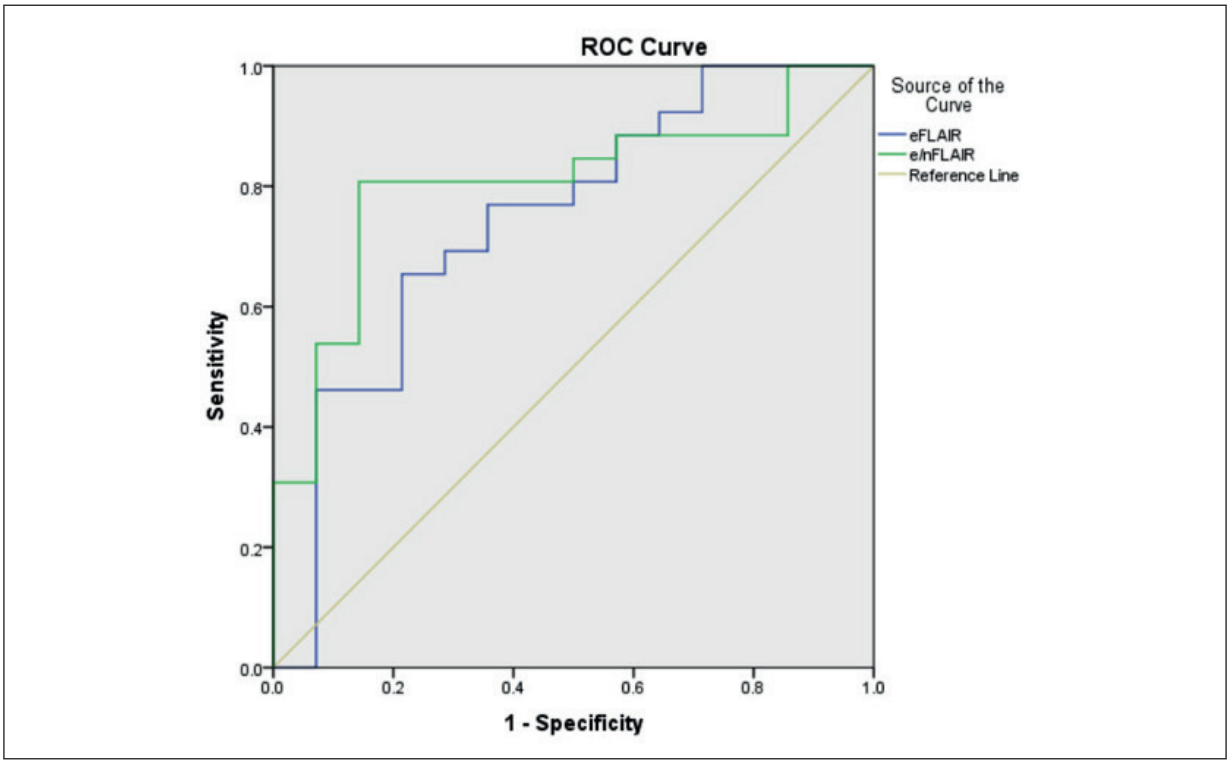

Figure 3. Receiver operating characteristic (ROC) curve using the fluid-attenuated inversion recovery (FLAIR) signal intensity (SI) values obtained from the enhancing region of the tumor (eFLAIR) and the SI ratio between the enhancing region of the tumor and the contralateral normal white matter (e/nFLAIR) for the differential diagnosis between glioblastoma and solitary brain metastases.

blood-brain barrier disruption and the increased leakage of interstitial fluid from capillaries[19,20]. GBM is associated with the tumoral infiltration of the surrounding white matter; therefore, the peritumoral edema associated with GBM consists of both vasogenic edema and tumoral infiltration[20]. The surrounding edematous fluid, associated with SBM, diffuses into the normal white matter through colloidal osmotic pressure, resulting in a larger quantity of extracellular water compared to the edema associated with tumor cell infiltrates in GBM[16,19], which may explain the lower pFLAIR values obtained for GBM compared with SBM in our results ($p < 0.05$). The AUC was 0.71 for a cutoff value of 1,039.96, which allowed for the differentiation between the two tumor groups with a Se of 71.4% and a Sp of 80.8%. In addition, the p/nFLAIR ratio for GBM was lower than that for SBM, but the difference was not significant ($p > 0.05$). However, the study reported by Chen et al[20] showed opposite results, with the p/nFLAIR ratio in GBM significantly higher than that in SBM ($p < 0.05$) and an AUC of 0.725 when using a cutoff value of 2.88. Chen explained that this difference

Table IV. Diagnostic performance of FLAIR SI parameters in the differential diagnosis between GBM and SBM.

Parameters	Cutoff	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)
eFLAIR	808.11	0.75	65.4	78.6	75.3	69.4
e/nFLAIR	1.63	0.81	80.8	85.7	85.0	81.7
pFLAIR	1,039.96	0.71	71.4	80.8	78.8	73.9

FLAIR: fluid-attenuated inversion recovery; SI: signal intensity; GBM: glioblastoma; SBM: solitary brain metastases; AUC: area under the receiver operating characteristic curve; Se: sensitivity; Sp: specificity: PPV: positive predictive value; NPV: negative predictive value; e: enhancing region of the tumor; *p:* peritumoral region; e/n: SI ratio between the enhancing region of the tumor and the contralateral normal white matter.

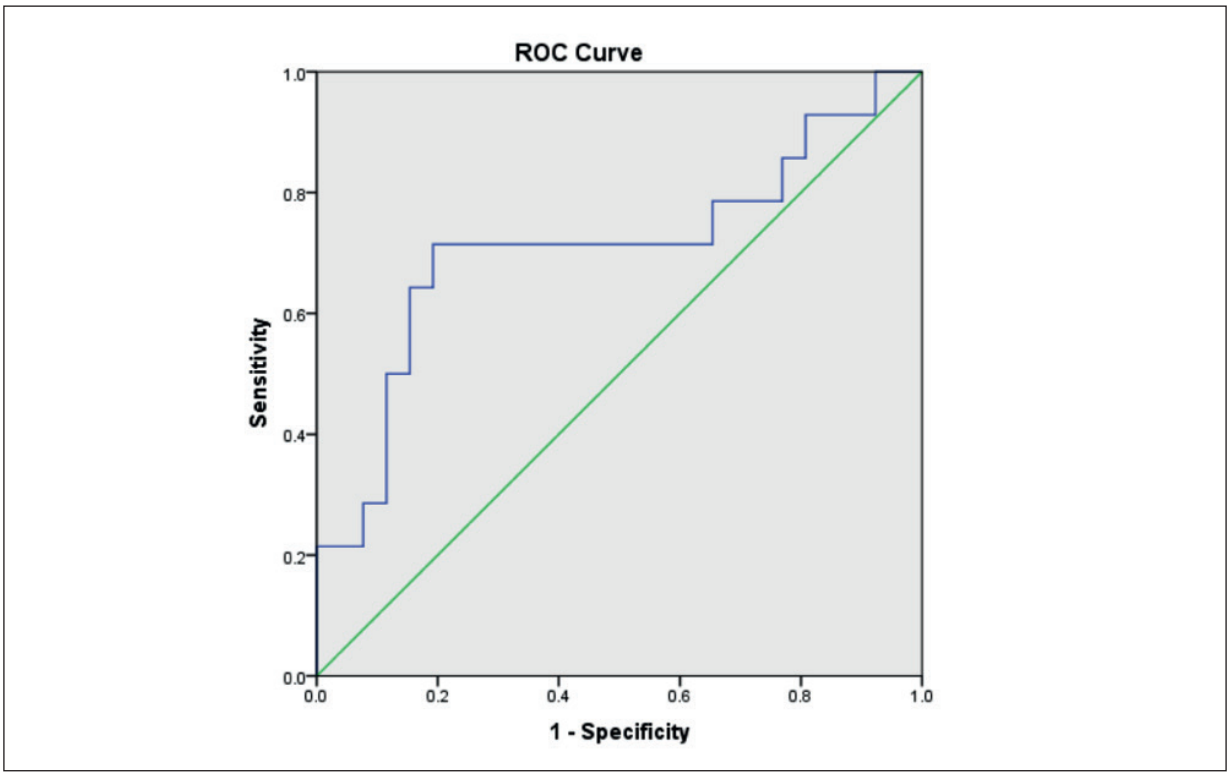

Figure 4. Receiver operating characteristic (ROC) curve using the fluid-attenuated inversion recovery signal intensity values obtained from the peritumoral region (pFLAIR) for the differential diagnosis between glioblastoma and solitary brain metastases.

might be due to the edema surrounding GBM reflecting not only invasive tumor tissue but also glial cell changes in the brain parenchyma.

To the best of our knowledge, no current quantitative research has examined the use of eFLAIR to differentiate GBM from SBM. Our study showed that the eFLAIR value of GBM was significantly higher than that of SBM ($p < 0.05$), and eFLAIR had an AUC of 0.75 when using a cutoff value 808.11, which allowed for the distinction between the two groups with a Se of 65.4% and a Sp of 78.6%. In particular, the e/nFLAIR ratios were significantly different between the two tumor types, with a higher diagnostic value, resulting in an AUC of 0.81, a Se of 80.8%, and a Sp of 85.7%. The higher eFLAIR values observed for GBM compared with SBM can be explained by the presence of degenerated microcysts, necrotic tissue, and tumor cell overgrowth in the extracellular matrix[8,21,22]. In addition, SBM originates from different tumor types, with varying histological characteristics depending on the primary tumor, which may introduce variation in the SI values associated with the tumor region.

Our study has some limitations. First, the retrospective study design and small sample size may not be sufficiently representative of the entire population of individuals with GBM or SBM. Furthermore, the sizes and locations of ROIs were different across cases. Both types of tumors are composed of tumor tissue and necrosis; therefore, a large ROI might measure non-tumor tissues, especially in cases where the enhancing tumor portion appears as only a thin border. However, a small ROI may not provide a sufficiently accurate signal value. In future studies, larger samples and advanced MR techniques could provide different results.

Conclusions

This study indicates that the quantification of FLAIR SI in GBM and SBM represents a convenient and effective method for distinguishing between these two types of tumors. GBM has significantly higher FLAIR SI values in the enhancing region but significantly lower SI values in the peritumoral edema region than SBM. The cutoff value of e/nFLAIR ratio of 1.63 was the most valuable indicator for the differentiation between GBM and SBM.

Ethical Approval

Ethical clearance was received from the institutional ethics committee of Hanoi Medical University (Ref: 2682/QD-ĐHYHN).

Informed Consent

The informed consent of patients was waived.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns, but are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no conflict of interests.

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Authors' Contributions

D.-H. Nguyen and D.-M. Nguyen contributed equally to this article therefore considered as first authorship. D.-H. Nguyen and M.-D. Nguyen prepared, drafted, and revised the manuscript critically, for important intellectual content. D.-H. Nguyen and M.-D. Nguyen contributed substantially to the acquisition, analysis, and interpretation of data. Each author gave final approval to the version of the manuscript submitted for publication and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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