Impact of Relative T2-FLAIR Signal Intensity of Non-Enhancing Lesions Outside Residual Cavity in Early Follow-up MRI on Outcome of Lower Grade Gliomas

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Abstract

Purpose T2-Fluid attenuated inversion recovery (FLAIR)hyperintensityoutside the residual cavity is one of the important MRI features in lowergrade gliomas (LGG), but its prognostic value needs to be further explored. The purpose of thisstudy was to investigate whether the relative signal intensity of T2-FLAIR outside the residual cavity (rFLAIR) can improve survival predictionofpost-treatment LGG patients or not.

Methods Clinical and pathological data, and early follow-up MR imaging of 152 patients with LGG were reviewed.We calculatedrFLAIRwith Image J software.Logistic analysiswas used to explore the significant clinicaland conventional MRI factors, and rFLAIR on progressionfree survival (PFS) and overall survival (OS).Different models were setup to predict survival prognosis of LGG.

Results Higher rFLAIR (1.80±0.84) of non-contrast-enhancing lesionsoutside residual cavity was detected in progression group (n=80) than that (1.55±0.33) of non-progression group (n = 72) (P<0.001)after radiotherapy.Multivariate analysis showed that higher rFLAIR(>1.595), as well as thick-linear and nodular enhancement of the residual cavity wall, were independent factors for the poor PFS and OS (both P<0.05). The cut-offrFLAIRof 1.595 could be used to predict poor PFS(HR 0.27, 95%CI 0.17-0.42) and OS (HR 0.22 95%CI 0.12-0.40)(P<0.001).Areas under the ROC curve (AUCs) for predicting poor PFS: clinical model 0.726, conventional MRI model 0.672, clinical + conventional MRI model 0.760, clinical + conventional MRI + rFLAIR combined model 0.827; AUCs for predicting poorer OS: clinical model 0.799, conventional MRI model 0.735, clinical + conventional MRI model 0.843, clinical + conventional MRI + rFLAIR combined model 0.880.

Conclusions Our preliminary results indicated that higherrFALIR (>1.595) of non-contrast-enhancing lesionsoutside the residual cavity can be used as a biomarker of poor survival of LGG. Moreover,rFLAIR is helpful to improve the survival prediction of post-treatment LGG patients.

Introduction

Although World Health Organization (WHO) grade II and III are grouped together as lower grade gliomas (LGG), they are actually heterogeneous group of cerebral primary neoplasm. Huge diversity exists for the survival outcome of LGGs owing to highly variable overall survival (OS) varied from 2.7 to 16.7 years [1] and different incidence of malignant transformation ranged from 23−72% [2]. An underlying assumption that individualized and more positive treatment, including targeted immunotherapy, re-irradiation, would improve survival state of LGG. But the interpretation of post-treatment imaging following standard chemoradiotherapy of LGG is still a challenge especially for those patients with no or minimal enhancement lesions [3].

In the new version of Response Assessment in Neuro-Oncology (RANO), the RANO-LGG criteria was developed. T2-weighted imaging (T2WI) / fluid attenuated inversion recovery (FLAIR) and post-contrast T1WI were still the basic sequences in follow-up MRI protocol of post-treatment LGG. Since relative lower incidence of enhancement of LGG, the follow-up MRI assessment is primarily based on T2/FLAIR changes. In RANO-LGG criteria, response and progressive lesions were determined mainly the decrease and increase of perpendicular diameters of T2/FLAIR hyper-intensity lesion outside residual cavity separately [4]. Bette et al [3] assessed overall FLAIR volume via manual segmentation. They found early FLAIR volume dynamic is an independent factor of LGG progression after treatment. Continuous follow-up MRIs, for example, 3 months or longer interval, are precise method for discrimination the residual tumor or progression from other pathologic changes. But the strategy "wait and see" needs long time to follow up and may lead to psychological torture to patients and delay of salvage therapy. On the other hand, the measurement of diameter or volume could not comprehensively reflect the pathophysiologic changes of residual T2-FLAIR hyperintensity, because the hyperintensity outside residual cavity may not only relate to residual tumor, but also due to nonspecific postoperative changes as well as ischemia. Previous studies suggested that functional MR techniques, such as perfusion imaging, proton MR spectroscopy (MRS), diffusion tensor imaging (DTI), and amide proton transfer (APT) imaging may be useful in distinguishing these conditions [5, 6]. Whereas, the application of advanced MR sequences is limited for their vague results as well as not being a routine exam in the clinic practice.

Therefore, the inability of the traditional visual inspection and T2/FLAIR percent change for detecting early progression of LGG would lead to delay the potential survival prolonging treatment strategies. We hypothesized that a quantitative method would be useful to characterize the evolution of residual T2-FLAIR hyperintensity. To the best of our knowledge, the role of quantitative metrics of T2-FLAIR hyperintensity outside the residual cavity in diagnosing survival outcome in LGG patients has not been investigated. In the present study, we retrospectively compared the relative signal intensity of T2-FLAIR outside the residual cavity (rFLAIR) between progressive and non-progressive post-treatment LGG patients. Additionally, we will evaluate the ability of rFLAIR in improving the survival prediction in combined prognosis model.

Methods

Patients

The study population included LGG patients who received treatment at our hospital for histologically confirmed astrocytoma and oligodendroglioma in grade II and III, and were treated according to the guideline of National Comprehensive Cancer Network (NCCN) [7] between April 2014 and December 2019. This study was approved by the Institutional Review Board. Since its retrospective nature, the informed consent from patients was waived. The inclusion criteria were: (1) gross-total resection of tumors and followed by radiation therapy and chemotherapy (CCRT) after operation and six cycles of adjuvant Temozolomide (TMZ) [8]; (2) with age older than 18-year-old [9]; (3) had undergone at least 3 times post-CCRTMR scans successfully, including < 72 h after operation, and before and after CCRT. (4) with survival follow-up for more than 12months. The exclusion criteria were: (1) only partial resection or biopsy was made; (2) with age less than 18-year-old; (3) with follow-up < 12 months; (4) with poor images quality; (5) without hyperintensity outside residual cavity; (6) had not received standardization treatment according to NCCN.

The patients' data, including demographics, pathologic diagnosis, treatment schedule, MR imaging data, and clinical outcomes were collected from hospital information system (HIS) (Fig. 1). Clinical information obtained included the dates of tumor resection and chemoradiotherapy, the dates of progression, and postoperative Karnofsky performance scale (KPS). Pathologic information collected included the histological type and grade of tumors, antigen identified by monoclonal antibody Ki-67, isocitrate dehydrogenase (IDH) mutation status, short chromosome 1 and long chromosome 19 arms (1p19q) status, and oxygen 6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status [10].

The LGG patients were divided into progressive and non-progressive groups according to RANO criteria [4]. The disease progression for grade II gliomas was diagnosed when one of the following criteria was met: (1) development of new lesions or increase of enhanced disease; (2) ≥25% increase in the sum of perpendicular diameters of the T2/FLAIR abnormality; (3) definite clinical deterioration. The definition of disease progression for grade III gliomas was based on one of the following criteria: (1) ≥25% increase in the sum of perpendicular diameters of contrasted lesion; (2) increase of the T2/FLAIR abnormality; (3) new enhancement disease; (4) definite clinical deterioration. From the date of surgery to the date of the last follow-up or death was defined as overall survival (OS). From the date of surgery to the date of progression or the date of the last follow-up without progression was defined as progression free survival (PFS) [11].

MR imaging and analysis

A 3-T MR scanner (PHILIPS MRI Systems Achieva, Best, the Netherlands) was used for serial follow-up MR imaging of all LGG patients. The follow-up MRI protocol included pre- and post-contrast transverseT1-weighted imaging (T1WI), transverse and sagittal T2-weighted imaging (T2WI), T2-FLAIR, post-contrast axial and sagittal and coronal T1WI. The parameters of T2-FLAIR included: slice thickness, 6.5mm; slice gap, 1.3mm; TR/TE, 9000/140ms; TI, 2600ms. The post-contrast T1WI (CE-T1WI) was made after injection of a standard dose (0.1 mmol per kilogram of body weight) of gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) at a rate of 3 mL/sec. The parameters CE-T1WI) included: 3D T1WI sequence; TR/TE, 6.7/3.3 ms; slice thickness, 1.2 mm; no slice gap. Follow-up MR examination was performed within 72h after tumor resection, before and at the end of radiotherapy, 3 and 6 months after radiotherapy. Thereafter, follow-up MR was made every 1 ~ 3 months depending on the enhanced disease and increase of hyperintensity lesions on T2-FLAIR images.

All MRI imaging data were collected from picture archiving and communication system (PACS). The conventional MR features analyzed included: the enhancement pattern of the residual cavity wall, new distal enhancement disease, new involvement of subventricular zone (SVZ). The enhancement of the residual cavity wall was categorized into three types: no enhancement; thin-linear enhancement (partial or entire wall enhancement with thickness <3 mm), thick-linear (partial or entire wall enhancement of 3 ~ 5mm thickness) or nodular (5 ~ 10mm in thickness) enhancement [12]. New distal parenchymal enhancement was defined as new enhanced disease that not contiguous (> 1.5 cm away from) with residual cavity or remnants of tumor after resection [13]. New SVZ involvement was defined as new enhancement lesions after standardized treatment on follow-up MRI.

The relative FLAIR signal intensity was measured with an open access image software, Image J(http://rsbweb. nih.gov/ij/docs/guide/). After input of FLAIR images into the software, we measured signal intensity in the following three region of interest (ROI): the hyperintensity disease outside residual cavity, contralateral cerebral parenchymal without abnormal signal intensity, background of the image (Fig. 2). All the measurements were made three times and the average value was recorded. rFLAIR was calculated as following formula: rFLAIR = (hyperintensity outside residual cavity- signal intensity of background) / (signal intensity of contralateral cerebral parenchymal without abnormality - signal intensity of background of image) [14]. The imaging findings analysis of follow-up MRI and measurement of signal intensity on FLAIR images were made independently by two neuroradiologists (with 6 and 18 year-experiences in diagnostic Radiology). When a disagreement existed, consent was reached after consulting another neuroradiologist with 26 year-experiences in neuroradiology.

Statistical Analysis

Statistical calculations were performed with the software IBM SPSS Version 21 and GraphPad Prism 8. The quantitative variables which were consistent with the normal distribution were reported as mean ± standard deviation. Those variables in non-normal distributions were reported as a median and an interquartile range. PFS and OS were created using Kaplan−Meier method and reported as 96% confidence interval (CI). Categorical variables were compared with Chi-square test between progressive and non-progressive groups, including quantitative clinical factors and conventional MRI findings. For comparing the difference of quantitative variables with normal distribution between progressive and non-progressive groups, we employed two independent samples t test. Otherwise, Mann-Whitney U test was used for comparison of non-normal distribution variables. The survival curves difference between different groups was compared using the results of the Log-Rank test. Multivariate Cox regression analysis was made for evaluation the risk factor for poorer survival and reported as hazard ratio (HR) in the form of 95% CI. Receiver operating characteristic (ROC) curve analysis was employed to determine threshold value and evaluation the diagnostic performance of different prognosis models with area under the curve (AUC), accuracy, sensitivity, specificity. P values less than 0.05 were considered statistically significant. Inter-readers' variability and repeated gray value measurement variability on FLAIR images was analyzed with intra-class correlation coefficient (ICC).

Results

In the 191 LGG patients initially screened, 39 patients were excluded for the following reasons: only diagnosed with biopsy (n = 4), age less than 18-year-old (n = 3), with incomplete MRI follow-up data (n = 15), with poor image quality (n = 2), without hyperintensity outside residual cavity (n = 10), had not received standardization treatment according to NCCN (n = 5). Finally, 152 patients were enrolled in this study, including 64 females and 63 males, aged from 18 to 73 year-old (45.06 year ± 1.01). Among 152 patients, there were 58 patients with grade II gliomas (25 with oligodendroglioma, 29 with astrocytoma, 4 with ganglioglioma), and 94 patients with grade III gliomas (39 with anaplastic oligodendroglioma, 55 with anaplastic astrocytoma). The gene phenotypes of these 152 patients were: isocitrate dehydrogenase (IDH) mutation status (94 patients, including 47 with IDH mutation, and 47 with wild type), short chromosome 1 and long chromosome 19 arms (1p19q) status 97 patients, including 40 with co-deleted, and 57 without co-deleted), oxygen 6-methylguanine-DNAmethyltransferase (MGMT) promoter methylation status (47 patients, including 34 with positive methylation and 13 without methylation). The enhancement patterns of the residual cavity wall included: 99 patients without enhancement or with thin-linear enhancement, 53 patients with thick-linear or nodular enhancement. New distal parenchymal enhancement was found for 8 patients and new SVZ involvement for 31 patients. There was no contrast enhancement lesion found in hyperintensity region outside residual cavity on FLAIR imaging in 120 patients (78.95%) in the first follow-up MRI after radiotherapy. The median follow-up time was 675 days (95% CI: 504−908 days).

The median progression-free survival (PFS) was 701 days [95% CI: 557–845 days] and median overall survival (OS) was 1311 days (95% CI: 962–1660 days). 47 patients (30.90%) were dead during the follow-up period.

Compared with non-progressive group, the variables were higher in progressive group included Ki-67 (0.20 vs 0.10, $P = 0.014$), grade III tumors (60.6% vs 39.4%, $P = 0.012$), wild-type IDH phenotype (72.3% vs 27.7%, $P = 0.012$), thick-linear or nodular enhancement of residual cavity wall (71.7% vs 28.3%, $P = 0.001$), new remote enhancement (100.0% vs 0.0%, $P < 0.001$), new SVZ involvement (83.9% vs 16.1%, $P < 0.001$), and rFLAIR (1.80 vs 1.55, $P < 0.001$). The KPS score (90.0) and incidence of 1p19q codeletion of non-progression group (75.0%) was higher than those of progression group (86.66 and 25.0% separately) ($P = 0.002$, $P = 0.007$). PFS of progression group (median, 387 days) was shorter than that of non-progression group (median, 656 days) ($P < 0.001$). Whereas, there was no significant difference of OS between progression and non-progression groups (686 days vs 656 days, $P = 0.524$). Neither for gender ($P = 0.945$), age ($P = 0.063$), radiation dose ($P = 0.283$), MGMT methylation status ($P = 0.285$) between the two groups [Table 1].

Table 1
Baseline characteristics of post-treatment patients with LGG ($n = 152$)

Characters	Non-progression ($n = 72$)	Progression ($n = 80$)	P value
Gender			
Male	40(47.6%)	44(52.4%)	0.945
Age (year)	43.13 ± 12.01	48.00(18)	0.063
Radiation dose (Gy)	59.92(6.00)	59.92(0.43)	0.283
KPS	90.00 ± 4.441	86.88 ± 7.394	0.002*
Ki-67	0.10(0.20)	0.20(0.20)	0.014*
WHO grades			
WHO grade Ⅱ	35(60.3%)	23(39.7%)	0.012*
WHO grade Ⅲ	37(39.4%)	57(60.6%)	
IDH gene phenotype			
Mutant	36(76.6%)	11(23.4%)	< 0.001*
Wild-type	13(27.7%)	34(72.3%)	
1p19q codeletion status			
Codeletion	30(75.0%)	10(25.0%)	0.007*
Non-codeletion	27(47.4%)	30(52.6%)	
MGMT methylation status			
Methylation	19(55.9%)	15(44.1%)	0.285
Non-methylation	5(38.5%)	8(61.5%)	
Enhancement pattern of residual cavity wall			
Non- or thin linear	57(57.6%)	42(42.4%)	0.001*
Thick-linear or nodular	15(28.3%)	38(71.7%)	
New remote enhancement			
No	72(50.0%)	72(50.0%)	0.006*
Yes	0(0.0%)	8(100.0%)	
SVZ involvement			
No	67(55.4%)	54(44.6%)	< 0.001*
Yes	5(16.1%)	26(83.9%)	
rFLAIR	1.55(0.33)	1.80(0.84)	< 0.001*
PFS (days)	656(391)	387(310)	< 0.001*
OS (days)	656(391)	686(432)	0.524

Note: LGG: lower grade glioma; Gy: gray; KPS: Karnofsky Performance Scale; IDH: isocitrate dehydrogenase; MGMT: oxygen 6-methylguanine-DNA methyltransferase; SVZ: subventricular zone; rFLAIR: relative FLAIR; PFS: progression free survival; OS: overall survival; Age in progression group, radiation dose, Ki-67 index, PFS, OS were in non-normal distributions and reported as a median and an interquartile range; *: represents a statistical difference.

Univariate analysis showed that elder (> 38 year-old), higher radiation dose (> 55Gy), lower KPS (≤ 85), higher Ki-67 index (> 0.275), grade III tumor, thicker linear and nodular enhancement, new distal enhancement, new SVZ involvement, and higher rFLAIR (> 1.595) were prognostic factors for poorer PFS and OS outcome (*P*<0.05 for all above variables). Survival analysis according rFLAIR was shown in Figs. 3A,B. Multivariate analysis showed that thick-linear and nodular enhancement and higher rFLAIR(> 1.595) were independent predictor for poor PFS (*P*<0.05), whereas, thick-inear and nodular enhancement, new SVZ involvement and higher rFLAIR (> 1.595)were independent predictor for poor OS (*P*<0.05) (Table 2).

Table 2
Survival analysis of patients with LGG

Characters	Univariate Analysis				Multivariate Analysis			
	PFS		OS		PFS		OS	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Age (year)	0.45[0.29;0.70]	0.002*	0.38[0.21;0.68]	0.006*	0.60[0.34;1.06]	0.076	0.68[0.30;1.52]	0.344
Radiation dose (Gy)	0.57[0.35;0.92]	0.041*	0.37[0.20;0.70]	0.018*	0.73[0.31;1.71]	0.468	1.58[0.36;6.82]	0.544
KPS	2.26[1.11;4.58]	0.002*	2.31[0.95;5.63]	0.012*	1.43[0.78;2.61]	0.244	1.56[0.74;3.30]	0.245
Ki-67	0.53[0.31;0.92]	0.008*	0.28[0.14;0.56]	< 0.001*	1.06[0.61;1.85]	0.832	0.58[0.30;1.14]	0.113
WHO grades	0.50[0.32;0.78]	0.004*	0.21[0.12;0.38]	< 0.001*	0.97[0.44;2.14]	0.939	0.37[0.08;1.73]	0.207
Enhancement pattern of residual cavity wall	0.35[0.21;0.59]	< 0.001*	0.20[0.10;0.28]	< 0.001*	0.48[0.27;0.87]	0.016*	0.36[0.17;0.74]	0.005*
New remote enhancement	0.24[0.06;0.95]	< 0.001*	0.25[0.06;0.99]	0.048*	1.02[0.41;2.50]	0.974	2.34[0.81;6.80]	0.117
SVZ involvement	0.31[0.16;0.60]	< 0.001*	0.22[0.10;0.50]	< 0.001*	0.61[0.34;1.09]	0.093	0.41[0.21;0.82]	0.011*
rFLAIR	0.27[0.17;0.42]	< 0.001*	0.22[0.12;0.40]	< 0.001*	0.29[0.16;0.55]	< 0.001*	0.31[0.12;0.83]	0.019*

Note: LGG: lower grade glioma; PFS: progression free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; Gy: gray; KPS: Karnofsky Performance Scale; SVZ: subventricular zone; rFLAIR: relative FLAIR; *: represents a statistical difference

Since the outcome of oligodendroglioma was considered more favorable than that of astrocytoma with same WHO grade [15], the survival outcome of these two tumors were compared furtherly. In this series, PFS of oligodendroglioma in grade II (1231 days) was longer than that of astrocytoma in grade II (862 days), the OS of oligodendroglioma in grade II (1503 days) was shorter than that of astrocytoma in grade II (1581 days). However, there was no significant difference between them (*P* = 0.164 for PFS, and *P* = 0.902 for OS). Similarly, PFS and OS of oligodendroglioma in grade III (726and 1311 days) were not different from those of astrocytoma in grade III (PFS, 486 days; OS, 852 days) (*P* = 0.285 and *P* = 0.334, separately) despite longer PFS and OS for oliodendroglioma patients.

ROC analysis showed that areas under the curve (AUCs) of different models for PFS were: clinical model 0.726, conventional MRI model 0.672, clinical + conventional MRI model 0.760, clinical + conventional MRI + rFLAIR combined model 0.827. Similarly, AUCs for predicting OS: clinical model 0.799, conventional MRI model 0.735, clinical + conventional MRI model 0.843, clinical + conventional MRI + rFLAIR combined model 0.880 [Table 3,Figs. 4A,B]. These results demonstrated that the diagnostic performance of survival outcome prediction would be improved when adding rFLAIR to combined model. Figures 3A,B show the Kaplan−Meier survival curves for PFS and OS according to the rFLAIR cutoff of 1.595. 5A-C show the classic examples of LGG patients with non-ehancing hyperintensity lesions in progression group.

Table 3
ROC curve analysis of different models in survival assessment of LGG patients

Characters	PFS			OS		
	AUC	95%CI	P value	AUC	95%CI	P value
Clinical	0.726	0.645−0.806	< 0.001[*]	0.799	0.725−0.873	< 0.001[*]
Con MRI	0.672	0.586−0.757	< 0.001[*]	0.735	0.642−0.829	< 0.001[*]
rFLAIR	0.710	0.626−0.795	< 0.001[*]	0.685	0.599−0.771	< 0.001[*]
Clinical + Con MRI	0.760	0.685−0.835	< 0.001[*]	0.843	0.722−0.915	< 0.001[*]
Con MRI + rFLAIR	0.799	0.729−0.868	< 0.001[*]	0.827	0.760−0.893	< 0.001[*]
Combined	0.827	0.763−0.891	< 0.001[*]	0.880	0.826−0.934	< 0.001[*]

Note: LGG: lower grade glioma; PFS: progression free survival; OS: overall survival; AUC: area under the curve; CI: confidence interval ; Clinical: including age, radiation dose, KPS, Ki-67, WHO grades; Con MRI: new remote enhancement, enhancement pattern of residual cavity wall and SVZ involvement; rFLAIR: relative FLAIR; Combined: Clinical, Con MRI and rFLAIR; [*]: represents a statistical difference.

The ICC of two neuroradiologists for diagnosing post-treatment progression based on RANO criteria was 0.945 (95%CI 0.924−0.960, P< 0.001). The agreement was also excellent between the two neuroradiologists for evaluation of MRI findings, including enhancement pattern of residual cavity wall (ICC,0.938; 95%CI 0.915−0.955), new distal enhancement (ICC,0.938; 95%CI 0.915−0.955, P< 0.001), new SVZ involvement (ICC, 0.942; 95%CI 0.920−0.958, P< 0.001), rFLAIR (ICC,0.989; 95%CI 0.986−0.992, P< 0.001).

Discussion

In this study, we analyzed the signal intensity outside residual cavity on FLAIR imaging of LGG patients with gross-total tumor resection. The present study indicates that the reproducibility for measurement of relative signal intensity on FLAIR images with the open-source software Image J. We showed that higher rFLAIR value (> 1.595) is an adverse prognostic factor for post-treatment progression and survival prognosis in LGG patients. Our data strongly supported the hypothesis that the ability of the quantitative metrics, the rFLAIR, in improving the survival prediction in combined prognosis model. Thus, besides the extent of hyperintensity disease, the relative gray intensity outside residual cavity on FLAIR images should be evaluated for post-treatment LGG patients.

The present study showed that the open-source software Image J could offer the quantitative metrics of FLAIR images with satisfactory reproducibility. As a widely used image-processing platform, Image J has already employed in biological image analysis for depicting weak signal variation beyond naked eye [16]. Image J had previously been used in the evaluation pontine glioma. In one series of 121 pediatric patients with post-treatment diffuse intrinsic pontine glioma (DIPG), Poussaint et al. generated quantitative metrics from FLAIR image and ADC map [17]. They demonstrated that pre-radiotherapy FLAIR skewness

and standard deviation were associated with shorter PFS. In the new version of WHO classification of CNS tumors (5th edition, 2021) [17, 18], DIPG would mainly be diffuse midline glioma with H3K27-altered, which is a kind of high-grade glioma with poor prognosis. In comparison, we analyzed rFLAIR of LGG in cerebral parenchyma in the present study. However, both our results and the study of Poussaint et al. demonstrated the usefulness of Image J in quantitative analysis of FLAIR image in post-treatment gliomas with different grades.

There were several advantages of this method. Firstly, we calculated the relative signal gray value by comparing the gray intensity of hyperintensity lesions outside residual cavity with contralateral parenchyma as well as background of the image, instead of directly measuring signal intensity on certain MR equipment. Thus we deduce that the bias came from different parameters of FLAIR sequence of various scanners and diverse magnet field strength could be averted. Secondly, tumor progression after LGG treatment was evaluated RANO criteria, which mainly based on T2-FLAIR disease. LGG, especially WHO grade II gliomas often manifested as T2-FLAIR hyperintense lesions without enhancement after gadolinium contrast medium injection [4]. Therefore, evaluation of these non-enhancing FLAIR hyperintensity lesions is critical for the therapy regimens of WHO grade II and III gliomas [3]. Thirdly, there was significant difference of rFLAIR between the progression (1.80) and non-progression groups (1.55) in this study. The rFLAIR, and the combined model including rFLAIR, could effectively predict poor survival outcome. Therefore, rFLAIR may be an adequate surrogate metrics and even eliminate a long-term follow-up when a suspected non-enhancing FLAIR hyperintensity lesion is found. Finally, antiangiogenic agents, including bevacizumab and cediranib, had been extensively used in the treatment of gliomas. These agents may lead to pseudo-response for temporally decreasing the permeability of blood-brain barrier and consequently diminishing contrast enhancement [19]. However, T2-FLAIR imaging could be used to detect the increase of non-enhancing hyperintensity lesion and thus could be used to identify early tumor progression.

Higher rFLAIR outside the residual cavity is probably due to neoplastic cell infiltration or tumor remnant. In one study which included 10 patients with WHO grade II-IV gliomas, Amjad et al. investigated the so-called peri-tumoral high signal regions on FLAIR imaging with functional MR techniques and targeted biopsy [20]. They found tumor cell infiltration and tumor core in 75% samples in FLAIR hyperintense regions. Thus, tumor cells have a tendency to infiltrate and manifest as non-enhancing T2-FLAIR hyperintense lesions. Although LGG is less aggressive than glioblastoma, Amjad et al. still confirmed that a portion of tumor extending outside the gadolinium contrast enhancing border in 7 patients with WHO grade II and III gliomas. These non-contrast-enhancing lesions could be visualized well on T2-weighted FLAIR imaging [21]. On the other hand, Chang et al. investigated the signal intensity outside the residual cavity on T2-FLAIR imaging and found small but significant changes could be detected months before the development of abnormal contrast enhancing lesions [22]. We also confirmed that new enhancing-lesions developed on follow-up MRI within the earlier non-contrast-enhancing hyperintensity region on FLAIR imaging. For standardizing the intensity value of FLAIR images among patients, Chang et al. employed a histogram normalization algorithm [22]. Whereas, we normalized the measurement of signal intensity on FLAIR images with comparing the gray value of non-contrast-enhancing lesions with contralateral parenchyma as well as background. The calculation method of rFLAIR in this study may be in favor of eliminating the influence of diverse scan parameters and different magnet fields on FLAIR imaging. Therefore, rFLAIR in non-contrast-enhancing lesions outside the residual cavity of LGG can be used as an imaging marker for estimating the burden of microscopic non-enhancing tumor and predict the location of recurrent disease in post-treatment LGG patients.

In the present study, we also confirmed prognostic prediction value of other previously described MRI features [9, 14, 23], including the enhancement types of residual wall and new distal enhancement and new SVZ involvement. However, the prediction performance of these feature was relative lower (AUC of 0.672 for PFS, AUC of735 for OS) and would be improved when combined with rFLAIR (AUC of 0.799 for PFS, AUC of 0.827 for OS). This phenomenon may be explained by the gliomas enrolled with lower grade in this study. The above mentioned MRI features could be detected more often in those post-treatment glioblastoma patients [12, 13]. The incidences of thick-linear and nodular enhancement (34.87%), new distal enhancement (5.26%), new SVZ involvement (20.39%) were lower than those of glioma (51.52%, 25.43%, and 49.14% separately) [12, 13]. On MRI, LGG often manifested as ill-defined hyperintensity T2-FLAIR lesions and without post-contrast enhancement because of less invasive, less angiogenesis and minimal disruption of blood-brain barrier [4]. New involvement of SVZ could be manifested as both new enhancement and non-enhancing FLAIR hyperintensity lesions in SVZ region. In this study, new SVZ involvement was detected as non-enhancing hyperintensity T2-FLAIR lesions in 80.65% patients (25/31). SVZ could increase invasiveness and migratory potential because it is the source of tumor precursor stem cells [11, 23]. Thus, higher incidence of SVZ involvement

(83.69%) in progression group in the present study, even without post-contrast enhancement, had adverse impaction on survival outcome of LGG patients.

Our data also confirmed that previously reported clinical factors, including age, post-operative KPS score, Ki-67 scores, WHO tumor grades, were associated with survival outcome of LGG [8, 10, 24, 25]. Previous studies had already identified that age was an important prognostic factor of gliomas. In an analysis of 113 grade III glioma patients, Hong et al. found 51 and 55 years old were the cutoff values of PFS and OS separately [8]. In the present study, we confirmed that the patients in progression group (48.00 year-old) were elder than those in non-progression group (43.13 year-old). The prognostic value of Ki-67 index for LGG was similar to that for glioblastoma [25] since higher Ki-67 index in LGG was associated with malignant transformation and poor survival outcome. We also found the Ki-67 index in progression group (0.20) was higher than that of non-progression group (0.10) ($p = 0.014$). However, our study revealed that the superiority of the outcome diagnostic performance with the combination of conventional MRI and rFLAIR (AUC of 0.799 for PFS, and AUC of 0.827 for OS) to those of clinical factors (AUC of 0.726 for PFS, and AUC of 0.799 for OS). Thus, we further combined conventional imaging findings with the quantitative metrics of FLAIR images, rFLAIR, which can be more reliable in differentiating tumor progression from non-progression patients with non-enhancing hyperintensity lesions outside residual cavity. This combination improved the prognostic prediction performance effectively. Therefore, we recommend that LGG patients with suspicious non-enhancing hyperintensity lesions on T2-FLAIR images should additionally calculate the quantitative metrics from conventional MRI sequence, such as rFLAIR.

Several limitations should be mentioned to the present study. First, although we revealed that the rFLAIR was independent prognostic factor of post-treatment LGG,the sample in this retrospective study was relatively small. We enrolled the consecutive LGG patients who had operated in a period of five years. But, because of relatively lower incidence (43.2% of all gliomas) [26] and comparative more benign course, LGG was less often encountered and treated aggressively in clinical practice. Thus, the results of this study warrant further validation with larger multicenter investigation. Second, as a retrospective analysis, there may be a selection bias of the patients. A few cases were excluded because of lost follow-up, without hyperintensity of FLAIR images, without standard treatment and follow-up measurement and so on. Third, the discrimination of progression from non-progression lesions was based on follow-up data except 9 patients who were confirmed as progression disease by re-operation. Fourth, we measured T2-weighted hyperintensity lesions in single ROI without discrimination tumor remnants from post-treatment cerebral edema, ischemic change. We confirmed that some FLAIR hyperintesity lesions were due to cerebral edema and ischemia based on the decrease in size of lesions with a long-term follow-up. Whereas, as a consequence of operation, ischemia plays an important role in inducing hyperintensity on T2-FLAIR imaging and probably leads to overestimation of tumor remnants [27]. Finally, although we collected molecular pathological data from some patients, including mutation of IDH, MGMT, and 1p19q co-deletion, molecular pathology examination has not been widely included in routine clinical examination in author's institution, especially in the era before 2016. Recently, Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy working committee considered that histologic grade II and III IDH wild-type astrocytic glioma should be referred as diffuse astrocytic glioma, IDH-wild-type, for these gliomas containing high-level EGFR amplification or TERT promoter mutations [26]. Further analysis on the outcome evaluation of LGG in the light of FLAIR hyperintensity lesions should be based on genetics of LGG in the future.

In conclusion, we found that higher rFALIR (> 1.595) of non-contrast-enhancing lesions outside the residual cavity was a useful predictor of poor survival of LGG. As one reproducible, accessible quantitative metrics based on conventional sequence, rFLAIR was helpful to improve the survival prediction of post-treatment LGG patients in clinical practice. An early post-treatment MRI performed after the completion of radiotherapy might be more appropriate for the delineation of tumor remnants in the region with non-enhancing hyperintensity on FLAIR imaging. The combination of rFLAIR, clinical factors and conventional MRI features may even eliminate a long-term follow-up for LGG patients when a suspected non-enhancing hyperintensity lesion is found.

Declarations

Conflict of interest The authors have no conflicts of interest.

Ethical approval This project was approved by Institutional Review Board of The Second Hospital of Hebei Medical University.

Data Availability Statement All data generated or analyzed during this study are included in this article.

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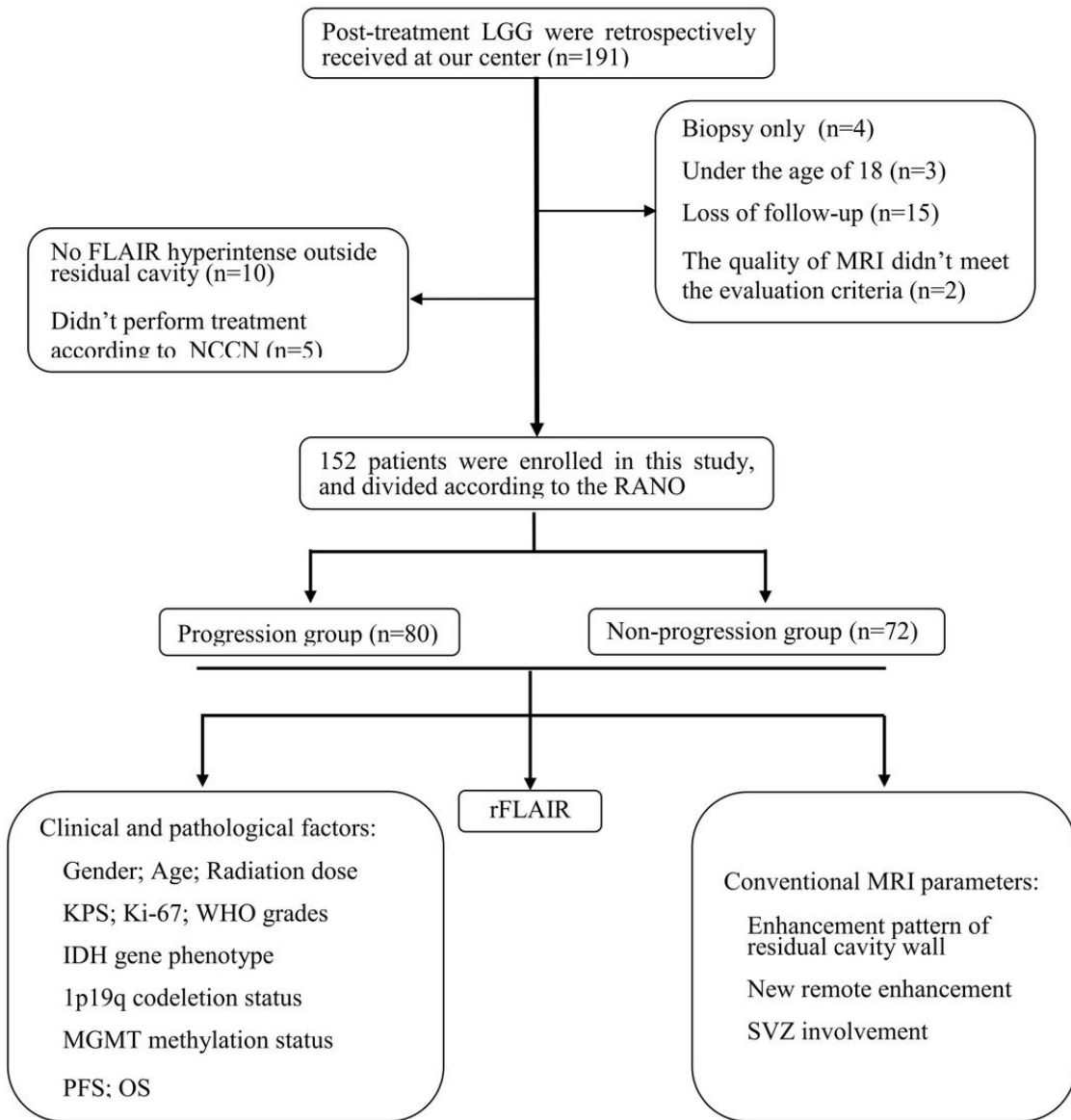
Figures

Figure 1

Patient flowchart. Note: IDH: isocitrate dehydrogenase; KPS: Karnofsky performance scale; LGG: lower grade glioma; MGMT: oxygen 6-methylguanine-DNA methyltransferase; NCCN: national comprehensive cancer network; OS: overall survival; PFS: progression free survival; RANO: Response Assessment in Neuro-Oncology; rFLAIR: relative FLAIR; SVZ: subventricular zone.
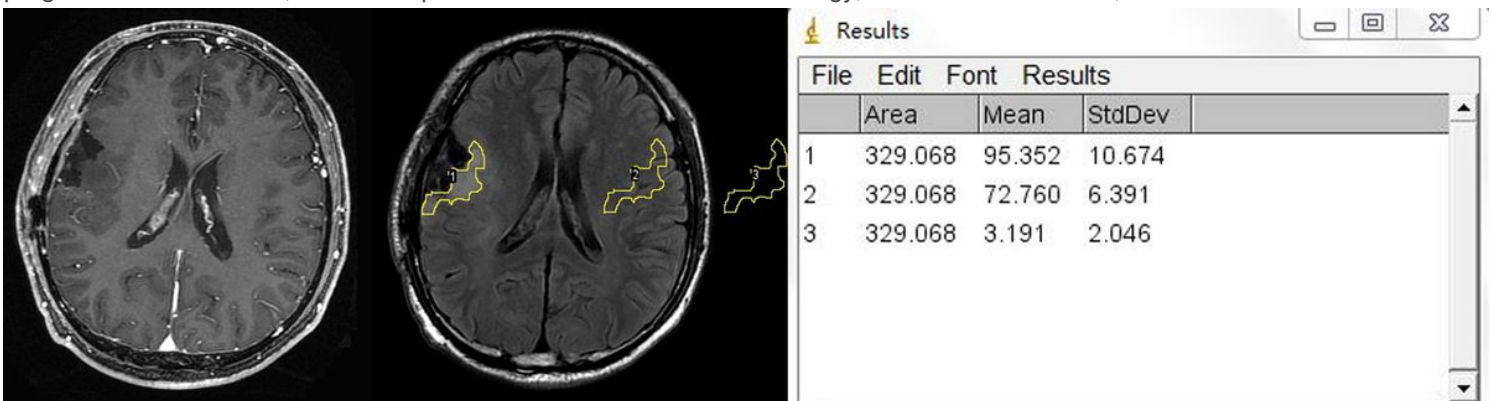
Figure 2

Example of ROI placement in a 54-year-old male with diffuse astrocytoma, IDH mutant. The PFS and OS were 907 days and 1044 days, respectively. Left figure: CE-T1WI shows no enhancement around the residual cavity. Middle figure shows 3 ROIs are placed in hyperintensity lesion outside residual cavity, contralateral parenchyma, and background of the image separately. Right figure shows the measurement output of Image J.
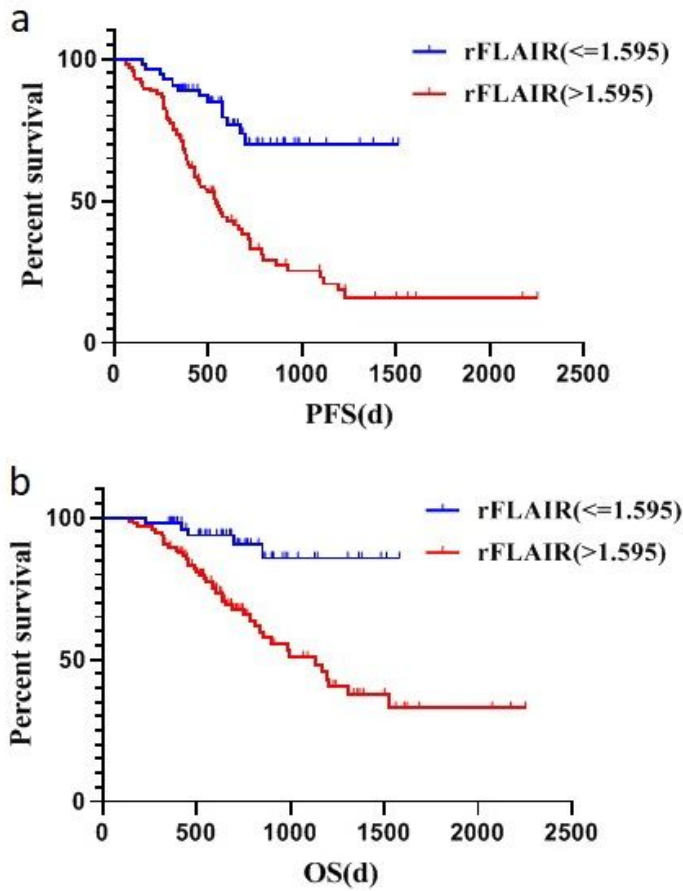

Figure 3

Kaplan–Meier estimates survival of post-treatment LGG patients based on rFLAIR. Fig. 3A, PFS. Fig.3B, OS. Notes: d: day; LGG: lower grade glioma; OS: overall survival; PFS: progression free survival; rFLAIR: relative FLAIR.
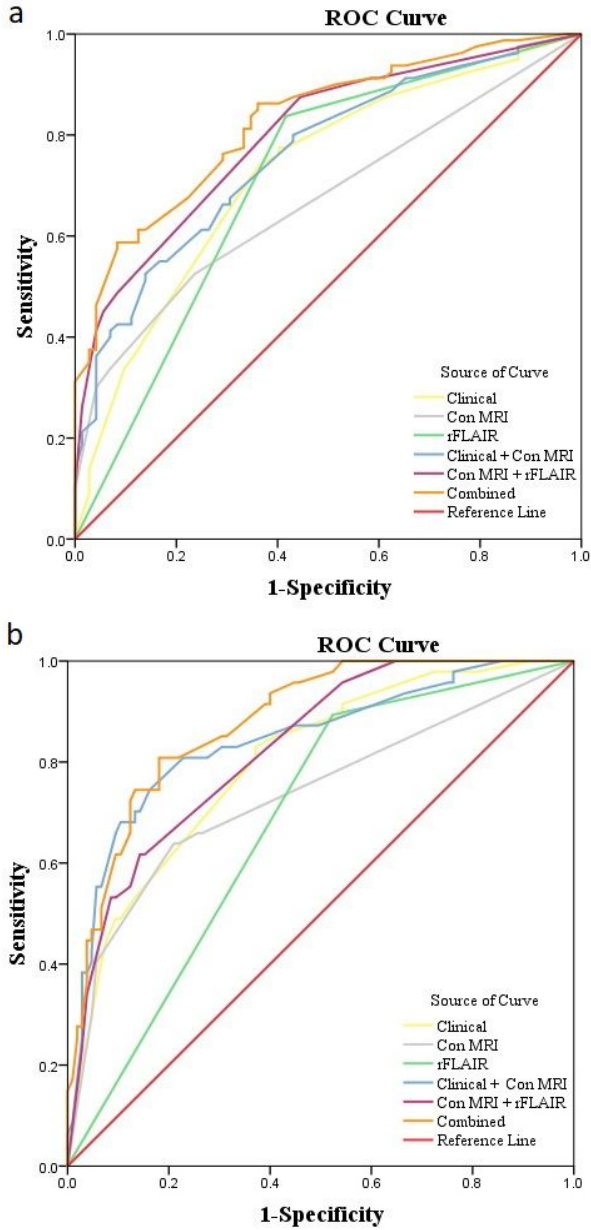
Figure 4

ROC analysis of different factors in survival assessment of LGG patients. Fig. 4A ROC for PFS. Fig 4B ROC for OS. Notes: Clinical: including age, radiation dose, KPS, Ki-67, WHO grades; Combined: including Clinical, Con MRIfindings, and rFLAIR; Con MRI: including new remote enhancement , enhancement pattern of residual cavity wall and SVZ; LGG: lower grade glioma; OS: overall survival; PFS: progression free survival; rFLAIR: relative FLAIR; ROC: area of curve
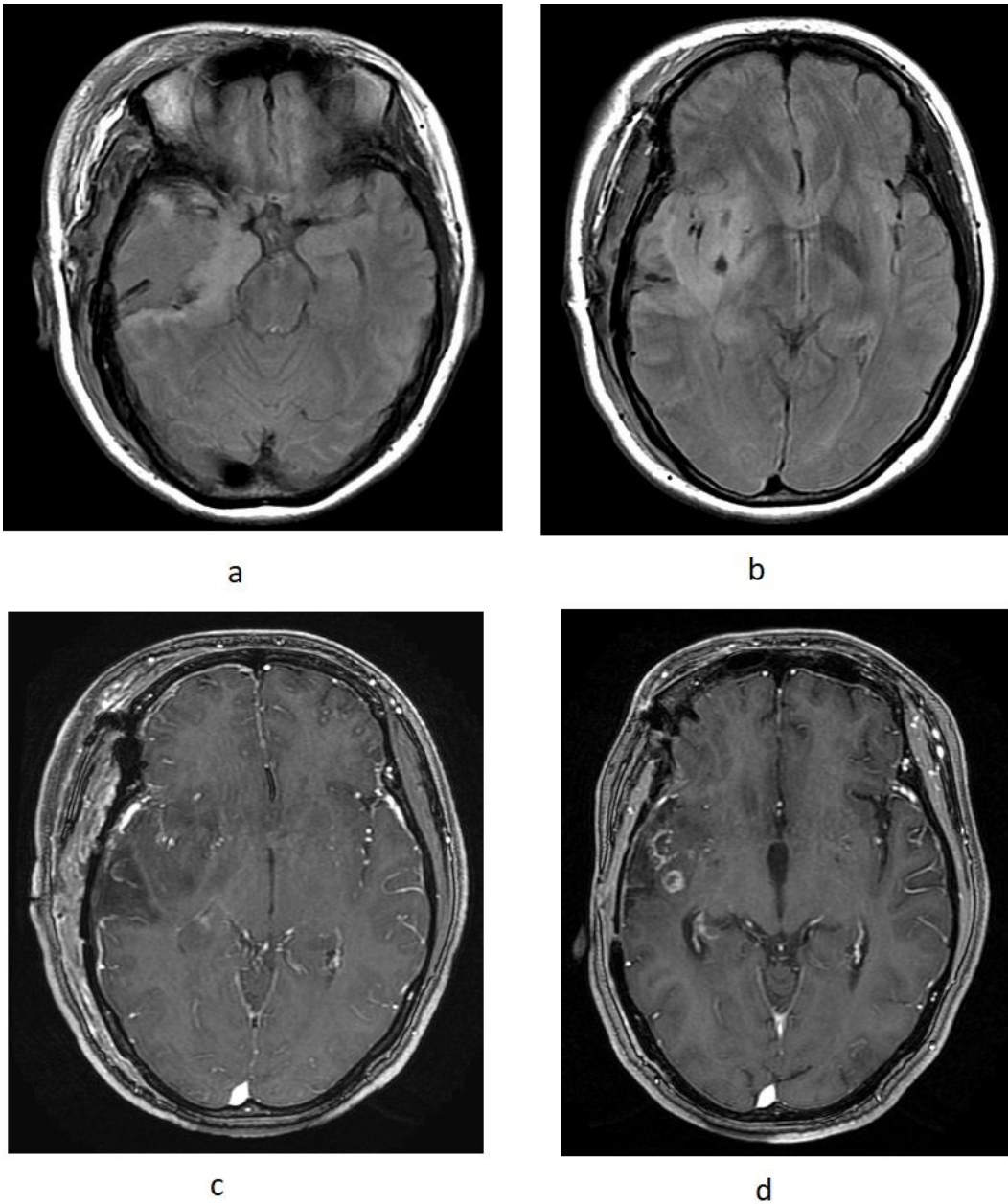
Figure 5

A 34-year-old male with diffuse IDH wild-type astrocytoma in his right temporal lobe. The PFS and OS were 339 days and 731 days, respectively. Fig 5A-C First follow-up MRI after completion of radiotherapy. Fig. 5A, B Axial FLAIR images show the residual cavity and the surrounding hyperintensity lesion. Fig. 5C Axial CE-T1WI does not show enhancement in the region corresponding to FLAIR hyperintensity. Fig. 5D Follow-up CE-T1WI 25 months after radiotherapy shows new developed ring and curved linear enhancement outside the residual cavity.