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Identifying the association between contrast enhancement pattern, surgical resection, and prognosis in anaplastic glioma patients

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Abstract

Introduction Contrast enhancement observable on magnetic resonance (MR) images reflects the destructive features of malignant gliomas. This study aimed to investigate the relationship between radiologic patterns of tumor enhancement, extent of resection, and prognosis in patients with anaplastic gliomas (AGs).

Methods Clinical data from 268 patients with histologically confirmed AGs were retrospectively analyzed. Contrast enhancement patterns were classified based on preoperative T1-contrast MR images. Univariate and multivariate analyses were performed to evaluate the prognostic value of MR enhancement patterns on progression-free survival (PFS) and overall survival (OS).

Results The pattern of tumor contrast enhancement was associated with the extent of surgical resection in AGs. A gross total resection was more likely to be achieved for AGs with focal enhancement than those with diffuse ($p = 0.001$) or ring-like ($p = 0.024$) enhancement. Additionally, patients with focal-enhanced AGs had a significantly longer PFS and OS

than those with diffuse (log-rank, $p = 0.025$ and $p = 0.031$, respectively) or ring-like (log-rank, $p = 0.008$ and $p = 0.011$, respectively) enhanced AGs. Furthermore, multivariate analysis identified the pattern of tumor enhancement as a significant predictor of PFS ($p = 0.016$, hazard ratio [HR] = 1.485) and OS ($p = 0.030$, HR = 1.446).

Conclusion Our results suggested that the contrast enhancement pattern on preoperative MR images was associated with the extent of resection and predictive of survival outcomes in AG patients.

Keywords Anaplastic glioma · Contrast enhancement · Pattern · Survival · Magnetic resonance imaging

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Introduction

Anaplastic gliomas (AGs) are classified as grade III malignant gliomas by the World Health Organization (WHO). The disease subtypes include anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma. The 5-year survival rate of AG patients is less than 40 % despite multimodality treatments such as surgery and adjuvant therapy [1]. The established prognostic factors for AG patients include age at diagnosis, preoperative Karnofsky performance status score (KPS), and the extent of resection [2–4]. Radiological biomarkers have also been utilized for postoperative survival evaluation [5–9]. However, there remains a lack of literature on the role of preoperative magnetic resonance (MR) images in predicting the survival of AG patients.

Contrast enhancement is considered a specific radiologic feature of high-grade gliomas, based on the physiological consequences of the compromised blood-brain barrier. Previous studies have revealed the significance of contrast enhancement on patient survival. Ring-like enhancement observable

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on computed tomography (CT) is reportedly indicative of poor survival in AG patients [9]. A smaller contrast enhancing area volume has been shown to correlate with longer overall survival (OS) in recurrent AGs [10]. A complete resection of MR contrast-enhanced tissue independently improves the outcomes of patients with oligodendroglioma and anaplastic astrocytoma, irrespective of histological grade [11, 12]. The pattern of contrast enhancement represents the biological characteristic of a tumor and has been observed to vary significantly among individual cases. However, whether the pattern of contrast enhancement on MR images has any impact on the extent of surgical resection and prognosis of AG patients has not been thoroughly investigated. Therefore, the present study aimed to identify a potential association of the tumor contrast enhancement pattern with the extent of resection and survival outcome in patients with AG.

Materials and methods

Patients

The current study spanned the period between May 2007 and August 2010. Clinical and radiologic data of 268 patients with histologically confirmed AG (WHO grade III) were retrospectively collected from our institutional database. Clinical variables included age, sex, preoperative KPS, extent of resection, histopathology, history of seizure, and postoperative adjuvant therapy. The inclusion criteria were as follows: (1) age of ≥18 years, (2) available pre-surgical MR imaging scans (T1-weighted, T2-weighted, and post-contrast T1-weighted), and (3) no previous diagnosis of any brain tumor. Patients were excluded if they had undergone any prior craniotomy or biopsy. Histopathologic diagnoses, including anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma, were confirmed by two independent neuropathologists, who were blinded to patients' clinical information, according to the 2007 WHO classification of brain tumors. The adjuvant therapy was fractionated radiotherapy or chemotherapy using temozolomide. This study was approved by our Institutional Review Board, and written informed consent was obtained from all enrolled patients.

Image acquisition

Pre- and post-surgical MR images were acquired using the standard pulse sequence on a 3.0 T MR scanner (Siemens Trio, Siemens Healthcare, Erlangen, Germany). T2-weighted images were acquired using an echo time (TE) of 140 ms, a repetition time (TR) of 8000 ms, and slice thickness of 5 mm. Post-contrast T1-weighted images were acquired after injection of gadopentetate dimeglumine (Ga-DTPA Injection, Beilu Pharma, Beijing, China) at a dose of 0.1 mmol/kg, using

a TE of 15 ms, a TR of 450 ms, and slice thickness of 5 mm. Postoperative MR scans used to determine the extent of resection were acquired 48–72 h after surgery.

Identification of contrast enhancement pattern

Contrast enhancement of the tumor was assessed by two neuroradiologists who were blinded to patients' clinical data. Non-enhancing tumors were defined as no apparent hyperintensity observed on post-contrast T1-weighted images. Tumor enhancement was defined as an unequivocal increase in signal intensity observed on T1-weighted images following intravenous contrast administration. Patterns of contrast enhancement were categorized into three types according to the morphological properties of the largest enhanced tumor area on contrast-enhanced MR images. The categories were focal enhancement, defined as a largest enhancing focal diameter of ≤1.5 cm with a relatively smooth border; diffuse enhancement, defined as tumor enhancements with maximum diameters of >1.5 cm with rough borders; and ring-like enhancement, defined as cystic necrosis with peripheral enhancement (Fig. 1). Images with classification discrepancy between the two reviewers were re-evaluated by a senior neuroradiologist who decided the pattern category used in the study.

Evaluation of the extent of resection

The extent of resection was assessed by comparing the volumes of pre- and post-surgery T2 hyperintensity and contrast enhancement. Gross total resection (GTR) was defined as no visible contrast-enhancing tumor on postoperative MR images within 72 h after surgery; for tumors with no preoperative contrast enhancement, GTR was defined as removal of all abnormal hyperintense changes on preoperative MR images.

Statistical analysis

The chi-squared test was used to compare the distribution differences of each clinical variable or imaging feature between the contrast enhancement and non-contrast enhancement groups, and among patients with different tumor enhancement patterns. Additionally, log-rank analysis of Kaplan-Meier data was performed for the comparison of progression-free survival (PFS) and OS between patient cohorts. Factors showing significance on univariate analysis ($p < 0.05$) were further entered into multivariate analysis using the Cox proportional hazards ratio (HR) model. Non-enhancement, focal enhancement, diffuse enhancement, and ring-like enhancement were designated as 0, 1, 2, and 3, respectively on multivariate analysis.
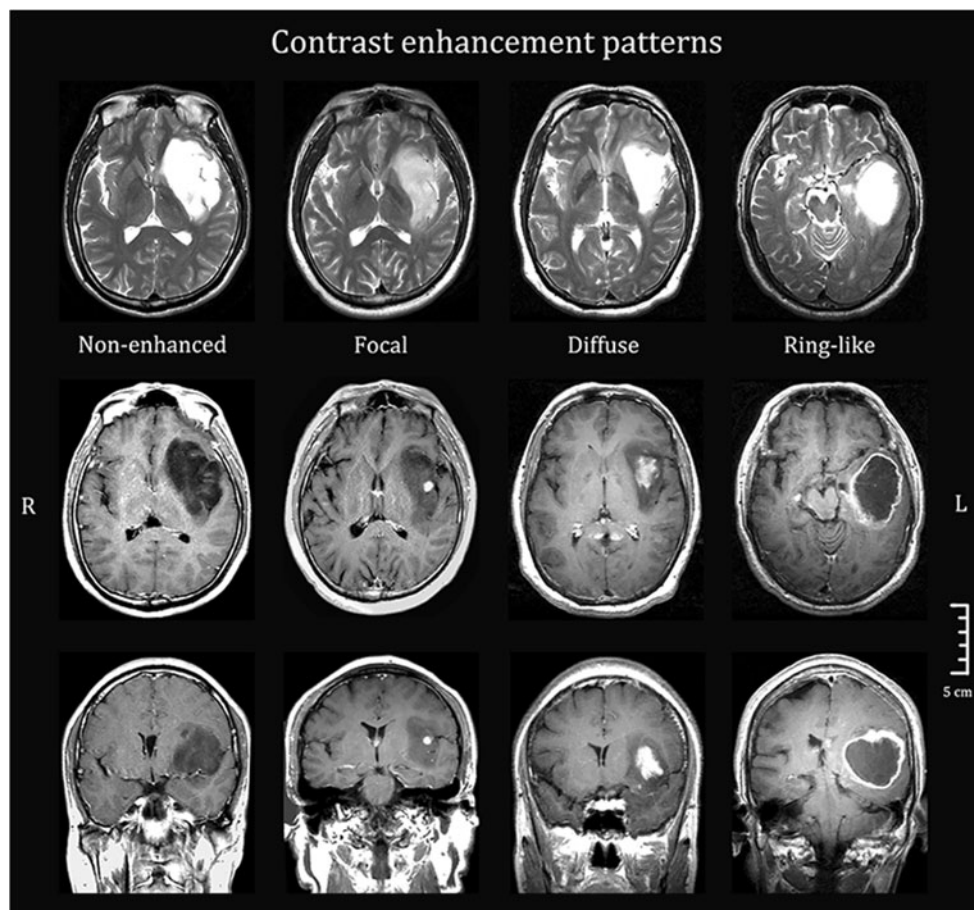
Fig. 1 Representative images of different tumor contrast enhancement patterns. T2-weighted (*top panel*) and post-contrast T1-weighted (*middle and bottom panels*) images of non-enhanced tumors and three different patterns of enhancement observed in anaplastic glioma

Results

Patient characteristics

A total of 268 AG patients were included in this study, including 73 cases of anaplastic astrocytoma, 47 anaplastic oligodendrogliomas, and 148 anaplastic oligoastrocytomas. Of these, 224 (83.6 %) tumors exhibited post-T1 contrast enhancement. The pattern of tumor contrast enhancement was reviewed for all patients, revealing 40 cases with focal enhancement, 80 with diffuse enhancement, and 104 with ring-like enhancement. The age at diagnosis, preoperative KPS, and extent of resection were significantly different among patients with different tumor contrast enhancement patterns ($p < 0.001$, chi-squared test; Table 1). Furthermore, 73 patients were diagnosed with anaplastic astrocytoma, 47 with anaplastic oligodendroglioma, and 148 with anaplastic oligoastrocytoma. Of all 268 patients, 212 (79.1 %) received radiotherapy and 165 (61.6 %) received chemotherapy.

The association between enhancement pattern and extent of resection

The kappa value for inter-rater agreement on enhancement patterns between the two evaluators was 0.93 ($p = 0.016$). In general, there were significantly fewer patients with contrast-enhancing AGs who achieved GTR than those with non-enhancing AGs (49.1 % vs. 68.2 % respectively, $p = 0.021$). Remarkably, the patterns of tumor contrast enhancement were found to be correlated with the extent of resection. A GTR was more likely to be achieved in patients with non-enhanced (68.2 %) or focal (70.0 %) enhanced AGs than those with diffuse (38.8 %) or ring-like (49.0 %) enhanced AGs ($p < 0.001$; Fig. 2). Of the enhanced AGs, focal-enhanced tumors were more amendable to surgical resection than diffuse ($p = 0.001$) and ring-like ($p = 0.024$) enhanced tumors. No significant differences in GTR rate were observed between AGs with focal enhancement and those without enhancement ($p = 0.857$), or between AGs with diffuse enhancement and those with ring-like enhancement ($p = 0.164$; Fig. 2).

Table 1 Clinical characteristics of all patients with anaplastic gliomas (n = 268)

Characteristics	Total of contrast enhancement (83.6 %) (n = 224)	Contrast enhancement			p value[a]	Non-contrast enhancement (16.4 %) (n = 44)	p value[b]
		Focal (14.9 %) (n = 40)	Diffuse (29.9 %) (n = 80)	Ring-like (38.8 %) (n = 104)			
Age (years)							
Median (range)	44 (18–87)	40 (21–71)	39 (18–67)	46 (18–87)		41 (18–63)	
≥50/<50	(27.2/56.4 %) 73/151	(5.2/9.7 %) 14/26	(6.7/23.2 %) 18/62	(15.3/23.5 %) 41/63	0.049	(2.6/13.8 %) 7/37	0.027
Sex							
Male/female	(51.1/32.5 %) 137/87	(7.1/7.8 %) 19/21	(19.8/10.1 %) 53/27	(24.3/14.5 %) 65/39	0.129	(11.2/5.2 %) 30/14	0.380
KPS							
≥80/<80	(60.1/23.5 %) 161/63	(12.7/2.2 %) 34/6	(23.9/6.0 %) 64/16	(23.5/15.3 %) 63/41	0.002	(14.2/2.2 %) 38/6	0.044
Extent of resection							
GTR/<GTR	(41.1/42.5 %) 110/114	(10.4/4.5 %) 28/12	(11.6/18.3 %) 31/49	(19.0/19.8 %) 51/53	0.005	(11.2/5.2 %) 30/14	0.021
Histopathology							
AA/AO/AOA	(22.0/15.7/45.9 %) 59/42/123	(2.2/2.6/10.1 %) 6/7/27	(8.2/6.8/14.9 %) 22/18/40	(11.6/6.3/20.9 %) 31/17/56	0.275	(5.6/1.5/9.3 %) 15/4/25	0.215
Radiotherapy							
Yes/No	(67.2/16.4 %) 180/44	(13.4/1.5 %) 36/4	(22.8/7.1 %) 61/19	(30.6/8.2 %) 82/22	0.194	(11.9/4.5 %) 32/12	0.255
Chemotherapy							
Yes/no	(51.9/31.7 %) 139/85	(10.4/4.5 %) 28/12	(15.7/14.2 %) 42/38	(26.1/12.7 %) 70/34	0.067	(9.7/6.7 %) 26/18	0.712

AA anaplastic astrocytoma, *AO* anaplastic oligodendroglioma, *AOA*, anaplastic oligoastrocytoma, *KPS*, Karnofsky performance scale score, *GTR*, gross total resection

[a] Chi-squared test of the three contrast enhancement pattern groups

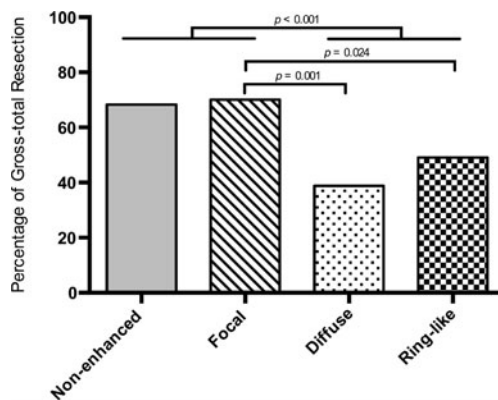[b] Chi-squared test between the contrast enhancement and non-contrast enhancement groups

Fig. 2 Gross total resection (GTR) rates for anaplastic gliomas (AGs) with different contrast enhancement patterns. GTR was more likely to be achieved in patients with non-enhanced or focal enhanced AGs than in those with diffuse enhanced or ring-like AGs ($p < 0.001$). Of the enhanced AGs, focal-enhanced tumors were more amenable to GTR than diffuse enhanced ($p = 0.001$) and ring-like enhanced ($p = 0.024$) tumors. No significant differences in GTR rates were observed between non-enhanced and focal enhanced AGs ($p = 0.857$) or between ring-like and diffuse AGs ($p = 0.164$)

Association between enhancement pattern, tumor location, necrosis features, and histology

The volumes and ratios of necrosis among patient groups with different enhancement patterns were compared. Volumes and ratios were both found to be significantly different among the three groups (Supplementary Table 1). Employing Fisher's Least Significant Difference test revealed that tumors with focal enhancement tended to have less volumes of necrosis than those with diffuse and ring-like patterns (Supplementary Table 2). Furthermore, tumors with focal enhancement showed lower ratios of necrosis than tumors with ring-like enhancement (Supplementary Table 3).

According to the histological features of AGs, tumors with and without oligodendroglial components were divided into two subgroups. The difference in proportions of contrast enhancement patterns between the two subgroups was statistically significant ($p = 0.042$). There was no significant difference in tumor location between AGs with and without an oligodendroglial component ($p = 0.389$), and the difference in subventricular zone involvement between the two

Table 2 Univariate analysis of survival outcome for patients with anaplastic gliomas (n = 268)

Characteristics	PFS			OS		
	p value	HR	95 % CI	*p* value	HR	95 % CI
Age (≥50 years)	<0.001	1.751	1.309–2.341	<0.001	1.756	1.284–2.403
Sex (male)	0.175	0.827	0.628–1.088	0.549	0.914	0.682–1.226
KPS <80	0.003	2.582	1.167–3.562	0.001	2.878	1.261–3.436
Enhancement pattern	0.002	1.408	1.214–1.800	0.023	1.406	1.106–1.832
Necrosis volume (>10 cm^3)	0.023	1.498	1.063–2.332	0.006	1.981	1.217–3.224
Ratio of necrosis (>0.1)	0.161	1.350	0.887–2.054	0.098	1.499	0.927–2.424
GTR/<GTR	0.004	1.560	1.155–2.107	<0.001	1.846	1.329–2.565
Histopathology	0.569	0.953	0.809–1.123	0.134	0.876	0.737–1.041
Radiotherapy	0.014	0.612	0.413–0.905	0.009	0.584	0.390–0.876
Chemotherapy	0.126	0.771	0.553–1.076	0.131	0.768	0.545–1.082

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance scale, *GTR* gross total resection

groups was also not statistically significant ($p = 0.465$) (Supplementary Table 4).

Predictors of survival outcome

During follow-up, 72.8 % of the enrolled patients experienced tumor recurrence, and 82 of 268 (30.6 %) patients with available follow-up data were alive; the median follow-up period was 43 months (range, 25–82 months). On univariate analysis, the age at diagnosis ($p < 0.001$), preoperative KPS ($p = 0.003$), tumor enhancement pattern ($p = 0.002$), necrosis volume ($p = 0.023$), extent of resection ($p = 0.004$), and radiotherapy ($p = 0.014$) were identified as prognostic factors for PFS, these five factors also showed prognostic value for OS (Table 2).

Significant differences in PFS and OS were observed among patients with AGs of different enhancing patterns (focal, diffuse, or ring-like; $p = 0.002$ for PFS and $p = 0.023$ for OS, log-rank; Fig. 3). Patients with a focal enhancing tumor

had a significantly longer PFS (median, 27 months) than those with a diffuse enhancing tumor (median, 19 months; log-rank, $p = 0.025$) or a ring-like enhancing tumor (median, 16 months; log-rank, $p = 0.008$). Similarly, patients with a focal enhancing tumor had a significantly longer OS (median, 30 months) than those with a ring-like enhancing tumor (median, 24 months; log-rank, $p = 0.011$) or a diffuse enhancing tumor (median, 27 months; log-rank, $p = 0.031$). There were no significant differences in PFS and OS between patients with a diffuse enhancing tumor and those with a ring-like enhancing tumor ($p = 0.159$ for PFS and $p = 0.278$ for OS, log-rank test).

Multivariate Cox regression analysis demonstrated that the pattern of tumor enhancement was a significant prognostic factor for PFS and OS in AG patients ($p = 0.016$ for PFS and $p = 0.030$ for OS). Other identified adverse prognostic factors for PFS included an age of ≥50 years, preoperative KPS of <80, necrosis volume >10 cm^3, and non-GTR. These variables were also independent prognostic factors for OS (Table 3).
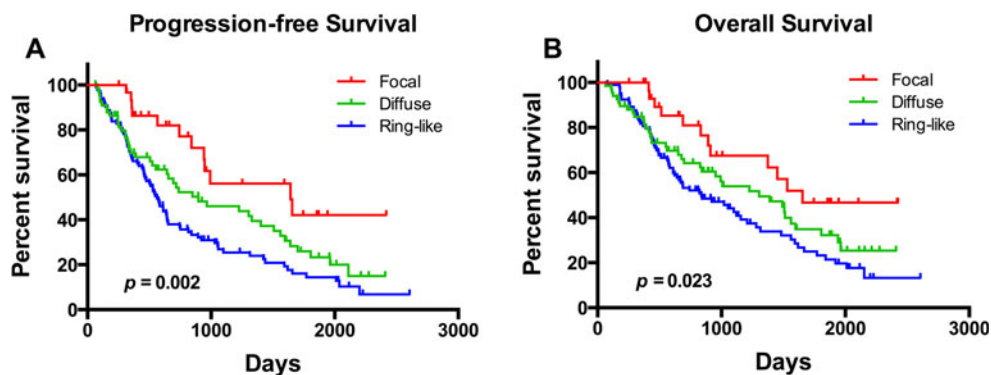

Fig. 3 Log-rank analysis of Kaplan-Meier curves demonstrated the differences in progression-free survival (PFS, $p = 0.002$) and overall survival (OS, $p = 0.023$) among patients with different tumor enhancement patterns. Those with focal-enhanced AGs had significantly better PFS and OS than those with diffuse ($p = 0.025$ and

$p = 0.031$, respectively) or ring-like ($p = 0.008$ and $p = 0.011$, respectively) enhanced AGs. No significant differences in PFS ($p = 0.159$) or OS ($p = 0.278$) were found between patients with diffuse enhanced tumors and those with ring-like enhanced tumors

Table 3 Multivariate analysis of survival outcomes for patients with anaplastic gliomas (n = 268)

Predictors	p value[a]	HR	95 % CI
PFS			
Age (≥50 years)	0.042	1.462	1.014–2.109
KPS <80	0.014	2.152	1.079–3.428
GTR/<GTR	0.004	2.076	1.266–3.405
Enhancement pattern	0.016	1.485	1.076–2.050
Necrosis volume (>10 cm^3)	0.047	1.698	1.007–2.864
OS			
Age (≥50 years)	0.045	1.483	1.009–2.180
KPS <80	0.026	1.827	1.021–3.613
GTR/<GTR	0.001	2.353	1.444–3.833
Enhancement pattern	0.030	1.446	1.036–2.019
Necrosis volume (>10 cm^3)	0.017	2.282	1.258–4.139

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance scale, *GTR* gross total resection

[a] Cox proportional hazard regression analyses

Discussion

This study retrospectively reviewed a large cohort of AG patients (*n* = 268). Specifically, the pattern of tumor enhancement was assessed as a radiological characteristic for all included patients. To our knowledge, the present study is the first to describe the association of tumor enhancement pattern on post-contrast T1 images with the extent of tumor resection and to identify such a pattern as an independent prognostic factor for AGs.

Several studies have revealed the association between aggressive surgical resection and improved survival in AG patients [4, 13–15]. More specifically, a complete resection of enhancing tissue was found to independently improve prognosis in enhancing oligodendrogliomas, irrespective of histological grade or genetic status [12]. For patients with anaplastic astrocytoma, the volume of residual tumor assessed on postoperative contrast-enhanced T1-weighted images was found to be a prognostic factor for PFS and OS [11]. Multivariable analysis in this study also showed that patients undergoing GTR had longer PFS and OS than those with residual tumors. A previous study found that GTR was more likely to be achieved in patients with more favorable tumor characteristics, such as a lack of contrast enhancement [16]. In this study, significant differences in GTR rates were observed between tumors with aggressive enhancement (diffuse and ring-like) and those with no or small (focal) contrast enhancement. Tumors without contrast enhancement or those that display focal enhancing areas disrupt the blood-brain barrier only to a limited degree, and tend to cause less damage to normal brain tissues than tumors exhibiting large areas of diffuse

contrast enhancement (e.g., diffuse or ring-like enhancement patterns). Tumors with no diffuse contrast enhancement or those with focal contrast enhancement are more likely to undergo GTR, and thereby indicate a better prognosis.

In addition to clinical characteristics, radiologic features such as contrast enhancing area and relative cerebral blood volume have been suggested to be associated with patient prognosis in high-grade gliomas [5, 10]. A previous study using CT scans demonstrated that ring-like enhancement was an adverse prognostic indicator in AG [9]. Nevertheless, the relationship between tumor enhancement pattern and patient survival outcome has rarely been investigated in AG. The present study addressed this issue by identifying the prognostic value of tumor enhancement patterns in AG patients via both univariate and multivariate analyses. We proposed some possible explanations for these results. First, the appearance of contrast enhancement is based on the blood-brain barrier disruption caused by tumor invasion. Ring-like contrast enhancement pattern indicates a rapid and aggressive proliferation of tumor cells that results in a necrotic core, which is considered to represent extreme malignant behavior and might lead to an unfavorable prognosis. As a common feature of malignant tumors, the extent of necrosis is important for the histological grading of gliomas because of its correlation with poor prognosis [17]. Previous studies showed that necrosis was correlated with the deletion of *CDKN2A*. Furthermore, anaplastic gliomas showing ring-like enhancements that are indicative of necrosis have been associated with worse survival outcomes [9, 18, 19]. Similarly, tumors with diffuse enhancement, which represents larger areas of damaged brain tissue and immature blood vessels, could possibly have a more invasive behavior than those with focal enhancement. Such differences may contribute to the variances in survival outcome. Second, many previous studies have identified the prognostic role of GTR in patients with high-grade gliomas [4, 13, 15, 20]. We found that GTR was more likely to be achieved in patients with focal tumor enhancement (70.0 %) than in those with ring-like (49.0 %) or diffuse (38.8 %) tumor enhancement (*p* = 0.005). Therefore, our findings suggested that the role of contrast enhancement pattern in survival prediction might partly be attributed to the prognostic effect by the extent of surgical resection. Finally, the prognostic role of tumor enhancement pattern might be associated with the variations in tumor genetic changes. Recent studies have demonstrated that various molecular subtypes of anaplastic oligodendroglioma, such as the pro-neural, mesenchymal, or neural subtypes, as well as 1p/19q co-deletion status, were associated with different radiological characteristics including tumor location, contrast enhancement, and heterogeneous intratumoral signals [6, 8, 21–23]. Moreover, patients harboring a tumor classified as pro-neural reportedly have a longer survival time compared to those with a mesenchymal subtype tumor [24–26]. Because it reflects the biological features of the tumor, the pattern of

tumor enhancement may indicate the genetic specificities that could potentially determine patient survival.

Factors that might influence the current results were considered. Different time intervals may be required for the maximum diffusion of contrast agent in tumor tissue. An appropriate scanning time was estimated at around 80 s following contrast agent injection by previous studies [27–29]. To minimize this potential heterogeneity, the time interval between injection of contrast agent and beginning of contrast-enhanced T1-weighted image acquisition was restricted between 75 and 85 s in this study. There are other factors that may influence tumor enhancement on MR images, such as equipment types and contrast agent concentration [30, 31]. In order to achieve a uniform criterion; all images were acquired using a 3.0 T MR scanner (Siemens Trio, Siemens Healthcare, Erlangen, Germany) in this study. Additionally, the contrast agent (Ga-DTPA Injection, Beilu Pharma, Beijing, China) used for all enrolled patients was obtained from the same pharmaceutical company.

Several limitations should be considered in the present study, including its retrospective design and lack of volumetric assessment. Although carefully controlled, a slight discrepancy in the time interval from contrast agent injection to scanning may still exist among individual patients. Such a discrepancy could potentially affect contrast enhancement intensity, although its significance requires further investigation. Future studies are encouraged to investigate the association between contrast enhancement patterns and the genetic characteristics of tumors.

Conclusion

The present study retrospectively reviewed the clinical data of 268 AG patients. In addition to previously reported prognostic factors, this study was the first to demonstrate the association of tumor enhancement patterns with the extent of resection, PFS, and OS in AG patients. Our findings suggest that tumor enhancement patterns could be employed as a non-invasive radiographic marker for the prediction of survival outcomes in patients with AGs.3

Compliance with ethical standards We declare that all human and animal studies have been approved by the Ethics Committee at Beijing Tiantan Hospital, Capital Medical University, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

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