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Original Article

Tumor pseudoprogression and true progression following gamma knife radiosurgery for recurrent ependymoma

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Abstract

Background: Gamma knife radiosurgery (GKRS) has become an effective salvage therapeutic option for recurrent ependymomas. However, its effectiveness can be assessed only by neuroimaging before clinical deterioration occurs. We analyzed the evolution of post-GKRS magnetic resonance imaging (MRI) features and sought to establish the feasibility of timely appropriate clinical management of the recurrent tumors.
Methods: We retrospectively investigated 19 recurrent ependymomas of 11 patients treated with GKRS in our hospital from 1994 to 2013. All included tumors had sequential MRI at 3–6-month intervals, and tumor response was volumetrically calculated on consecutive MRI.
Results: Post-GKRS tumors might show an increased enhancement or loss of enhancement associated with tumor enlargement or straight shrinkage. Seven of 19 tumors (37%) had continuously regressed or remained stable up to the last follow-up. Twelve of 19 tumors (63%) showed enlargement of enhancing lesions through examination of the post-GKRS follow-up MRI within the first 18 months. Five of 12 tumors (42%) showed continuous enlargement, which was interpreted as true progression; seven of 12 (58%) exhibited transient increasing enhanced volume that resolved within 6 months, and which was interpreted as pseudoprogression. There was no significant association between the presence of pseudoprogression and the pathological grades or locations of the tumors, and the concomitant chemotherapy or previous radiotherapy. Statistically significant differences were found for mean apparent diffusion coefficient (ADC) values and ADC ratio (prior to and after GKRS) of enhancing lesions between pseudoprogression and true progression.
Conclusion: The MRI patterns of post-GKRS recurrent ependymomas are heterogeneous. Transient increased tumor volume may represent pseudoprogression, whose final tumor control rate was not significantly different from those cases with straight tumor shrinkage. ADC values, ADC ratio, and sequential follow-up MRI scans are beneficial to differentiate between pseudoprogression and true progression, and help guide clinical management.

Keywords: ependymoma; magnetic resonance imaging; pseudoprogression; radiosurgery

1. Introduction

Intracranial ependymomas are the third most common primary brain tumors in children[1] and constitute 4% of adult tumors.[2] Despite aggressive initial treatment, tumor recurrence is common, and treatment options of a recurrent ependymoma are often limited by previous therapies. Gamma knife radiosurgery (GKRS) has become an effective salvage therapeutic

Abbreviations: ADC, apparent diffusion coefficient; GKRS, gamma knife radiosurgery; MRI, magnetic resonance imaging; RT, radiation therapy.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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option for recurrent ependymomas. The effectiveness of treatment can be assessed only by neuroimaging prior to onset of clinical deteriorated. The purpose of this study was to evaluate the evolution of tumor response to GKRS and ascertain the feasibility of offering timely further appropriate management of these tumors, if clinical status warranted.

2. Methods

All aspects of the work covered in this manuscript followed the principles of World Medical Association Declaration of Helsinki. A total of 11 patients (19 tumors) with relapsed ependymoma treated by GKRS at our institute from 1994 to 2013 were included. All patients had undergone surgical tumor resection at the time of diagnosis, followed by sequential magnetic resonance imaging (MRI) at 3−6-month intervals for at least 12 months, and had new recurrent lesions revealed by follow-up MR images. We retrospectively reviewed the MR images and the clinical data, including patient age, tumor grade, tumor location, extent of surgical resection, and the treatment regimen. All tumors were classified according to the World Health Organization classification (2007).[3]

2.1. MRI

MRI was performed using 1.5-T clinical MRI scanners (GE Medical Systems, Milwaukee, WI, USA), with conventional circularly polarized head coils and intravenous administration of standard doses of gadolinium-based contrast. All tumor volumes were defined by neuroradiologists as the sum of tumor segmentation on all tumor slices based on Gd-enhanced spin-echo T1-weighted MRI (3-mm slice thickness, no gap). For each lesion, the same imaging protocol and volumetric measurement were applied at every follow-up time point.

Of the lesions that showed increased enhancing area after GKRS, absolute apparent diffusion coefficient (ADC) values of the tumor or enhancing lesions prior to and after GKRS were measured retrospectively by placing regions of interest delineated according to the tumor geometry on ADC maps with OsiriX MD imaging software version 7.0. We measured the lesions with an increased size of the enhancing area after GKRS, and obtained ADC ratios (ADC of the enlarged enhancing lesion after GKRS to ADC of the treated tumor prior to GKRS). Thereafter, the dynamic changes of post-therapeutic imaging patterns and the long-term volume changes were analyzed.

Tumor recurrence was radiologically defined as a new enhancing lesion with steady growth of enhancement and/or mass effect on follow-up MRIs. Pseudoprogression was radiologically defined as transient enlargement of an enhancing lesion followed by tumor regression on MRIs, and true progression was defined as persistent enlargement of an enhancing lesion on MRIs or pathologically verified through surgical resection. Local tumor recurrence was defined as a new enhancing lesion at the previous operative bed; infield recurrence after GKRS as a new enhancing lesion that occurred 2 years later at prior GKRS treated area; and distant recurrence as a new enhancing lesion at the site other than local tumor recurrence.

2.2. GKRS

Stereotactic radiosurgery was performed using the Gamma Knife (Leksell; Elekta, Inc., Atlanta, GA, USA). Transaxial and coronal contrast-enhanced T1- and T2-weighted imaging were used for dose planning of GKRS in all cases. In 17 tumors, the GKRS treatment volumes were defined according to the enhancing tumor components. In the other two patients, who had a nonenhancing tumor, the GKRS treatment volumes were based on T2-weighted imaging volumes. Contrast-enhanced T1-weighted imaging were acquired after bolus injection of contrast medium (0.1 mmol/kg) with a 3-mm slice thickness and no gap. The mean tumor volume was 3.02 (range 0.07−18.95) mL prior to GKRS. The tumor volume of the only grade II ependymoma case was 0.77 mL, and the mean tumor volume of grade III (anaplastic) ependymomas was 3.15 mL. The median prescription dose delivered to the margins of the tumor was 13 Gy (range, 12−24 Gy), at 55−68% isodose levels. A median of 10 isocenters (range, 4−21) per tumor was used for the GKRS.

2.3. Statistics

We used Fisher exact test and logistic regression for comparison of independent variables because some cells had low expected frequencies (fewer than 5). Local tumor control were estimated using Kaplan−Meier curves and a univariable log-rank test based on the dates of diagnosis, first GKRS session, follow-up MRI, and last follow-up or death. All statistical analyses were performed using SPSS (version 19.0; SPSS, Chicago, IL, USA), using two-sided statistical testing at the 5% significance level.

3. Results

The current analysis ultimately comprised 19 tumors of 11 patients, of whom six were male and five female, aged 2−45 (median 12) years. Histologic diagnosis of the primary site in these cases was as follows: one (9%) World Health Organization (WHO) grade II ependymoma, and 10 (91%) WHO grade III anaplastic ependymomas. Eight treated lesions were supratentorially (including 5 local and/or infield recurrences and 3 distant metastases) and 11 were infratentorially located (10 local recurrences and 1 distant metastasis). Subsequent to tumor resection, all but one patient underwent a full course of fractionated RT. Among them, six patients received cranial radiation only, and four patients also received neuraxis RT. Five patients had pre-GKRS chemotherapy. The median interval between RT and GKRS was 42 months (range, 4−131 months).

Seven of 19 tumors (37%) showed a post-GKRS straight decrease in the tumor size. Twelve of 19 tumors (63%) showed

enlargement of enhancing lesions at post-GKRS follow-up MRI within the first 18 months. Seven of the tumors (58%) were defined as pseudogression, and the other five (42%) were true progression. The onset of pseudoprogression was observed at 7.9 (4.8–10) months post-GKRS, and the onset of true progression was observed at 4.9 (3–8) months post-GKRS, respectively (Fig 1). The post-GKRS tumors showed persistent enhancement, increased enhancement or partial loss of enhancement, while the tumor volumes might be stable, decreasing or increasing (Figs. 2 and 3). Additionally, the enhancing patterns and tumor volumes might change over time. In the current study, there was no lesion of true progression showing persistent enhancement and there was no lesion exhibiting shrinkage or stability showing new enhancement after GKRS. However, the enhancing pattern at the time of tumor enlargement did not differ between tumors with pseudoprogression and true progression ($p = 0.92$). The age at GKRS, the pathological grades or locations of the treated tumors, whether concomitant chemotherapy or temozolomide was being used, the dose of previous RT, and the time interval between RT and GKRS did not differ significantly between pseudoprogression and true progression. The mean prescribed dose of GKRS, tumor volume at GKRS, and dose at tumor margins did not differ between pseudoprogression and true progression. All pseudoprogression of tumor except one decreased in size within a 6-month follow-up, whereas all lesions of true progression persisted and were enlarged on follow-up MRI scans ($p = 0.03$). One exceptional pseudoprogression showed tumor shrinkage after 30 months post-GKRS, and was the only WHO grade II ependymoma in the current study. In that case, the tumor size peaked at 15 months post-GKRS, and slowly regressed to a small enhancing nodule, which was smaller than the pre-GKRS tumor and remained stable up to 89 months post-GKRS. After excluding one case of pseudoprogression with post-GKRS intratumoral hemorrhage, and two cases without pre-GKRS diffusion-weighted images, absolute ADC values and ADC ratios were obtained and nine of the 12 tumors showed enlargement of enhancing lesions at the post-GKRS follow-up MRI. ADC values were significantly higher in lesions of pseudoprogression ($1.41 \pm 0.23 \times 10^3$ mm^2/s; mean ± standard deviation) than in true progression ($0.85 \pm 0.06 \times 10^3$ mm^2/s; $p = 0.002$). ADC ratios were also significantly higher in lesions of pseudoprogression (1.15 ± 0.11; mean ± standard deviation) than in true progression (0.92 ± 0.02; $p = 0.005$). The variables between the pseudoprogression and true progression groups are summarized in Table 1.

The mean local control time of GKRS was 28.9 (3–51) months. Kaplan–Meier curves generated for local tumor control showed that tumors with pseudoprogression features were associated with 1- and 2-year local control rates of 100% and 67%, respectively. Patients whose tumors had stable or decreased volume on MRI had 1- and 2-year progression-free survival rates of 100% and 100%, respectively. For true progression tumors, the 1- and 1.5-year tumor progression-free survival rates were 20% and 0%, respectively. The first 2-year local tumor control rate of pseudoprogression in patients who had pseudoprogression features on MRI was similar to those who had a stable or decreased tumor size ($p = 0.364$),

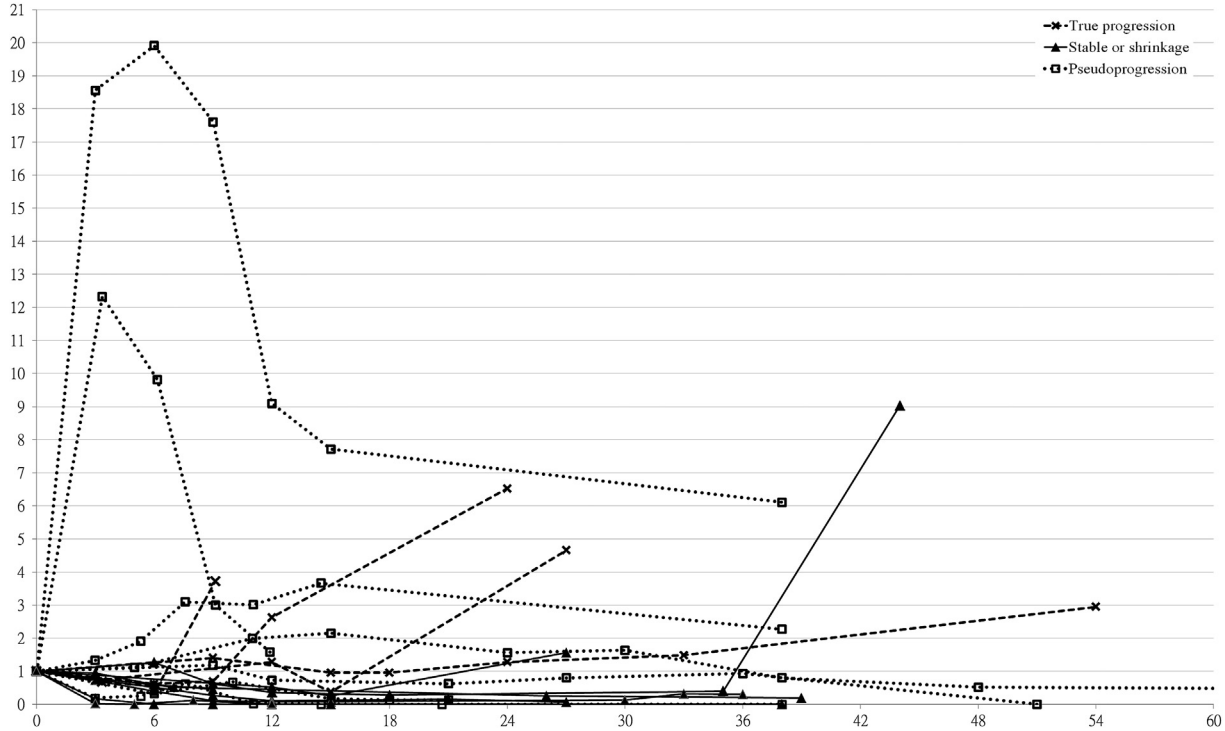

Fig. 1. Line plots of the volume change (in percentage) over time of the total 19 tumors after GKRS.

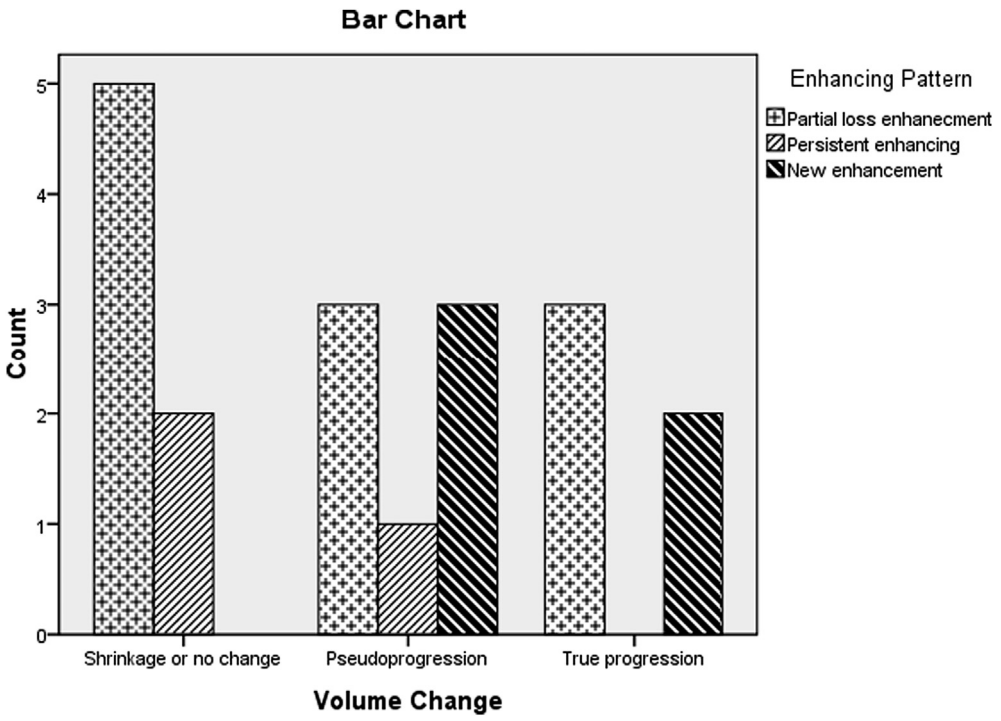

Fig. 2. Bar chart of enhancing pattern and volume changes after gamma knife radiosurgery in the 19 tumors.

whereas patients who had pseudoprogression or a stable or decreasing tumor on MRI exhibited superior local tumor control to that of patients who had true progression ($p = 0.006$) (Fig. 4).

4. Discussion

Ependymal tumors range in WHO grade classification from I to III,[3] and the clinical outcomes vary.[4,5] Relapsed ependymoma in children yields a poor prognosis, with a previously reported overall survival rate of 29% at 2 years.[6] Thus far, there remains a lack of novel targeted therapies and adequate systemic chemotherapy for a cure. Moreover, reoperation and re-irradiation are often limited and/or associated with increased difficulties caused by prior treatment. Since the late 1980s, stereotactic radiosurgery has been used and reported to be an effective alternative to repeated surgical resection or repeated external beam whole-brain RT in cases of relapsed disease,[7,8] and has been proven to provide effective local control and may improve survival rates for patients with limited recurrent disease in recent studies.[9–11] In the current study, the 1-year local control rate was 89%, and the 2-year overall-survival rate was 81%.

The treatment efficacy of GKRS can be monitored and evaluated only by neuroimaging. In contrast to conventional radiotherapy, GKRS is a highly precise and focused form of irradiation. The focused irradiation results in primarily local radiation-induced changes. In post-GKRS vestibular schwannomas, a transient increase in size followed by stability or regression has been increasingly recognized as treatment effects rather than treatment failures in the first post-GKRS 24 months. *Pseudoprogression* was recently adopted to describe the transient tumor volume increases of post-GKRS vestibular schwannomas.[12] Initially, the term *pseudoprogression* was applied to describe glioblastomas that developed transient tumor progressive deterioration on MRI scans after postconcomitant chemoradiation therapy with temozolomide.[13–16] The pathophysiological changes of pseudoprogression involved in post-GKRS schwannomas might be different from that of glioblastomas, although neither of the mechanisms of pseudoprogression has yet to be been fully elucidated. In glioblastoma, such mechanisms are believed to be due to a higher chemoradiation-induced degree of (desired) tumor-cell and endothelial-cell killing with an associated inflammatory reaction and abnormal vessel permeability in the tumor area.[13] In contrast, the biological effects of radiosurgery on vestibular schwannoma cells are believed to be a combination of acute inflammation and vascular occlusion or apoptosis.[17,18] Why this occurs mainly in schwannomas remains unclear. In the current series, we used the term of *pseudoprogression* to describe post-GKRS transient tumor volume enlargement of ependymomas, although the involved mechanism might be neither the same as glioblastomas nor schwannomas. Using sequential volumetric assessment, we demonstrated that a significant portion of post-GKRS ependymomas presented pseudoprogression within the first post-GKRS 12 months (58% in all 12 tumors showing initial enlargement or 37% of all 19 treated tumors). In contrast to post-GKRS vestibular schwannomas, of which the transient tumor enlargement mostly last longer than 1 year, all pseudoprogression of post-GKRS recurrent anaplastic ependymomas regress within 6 months. In the future, if tumor

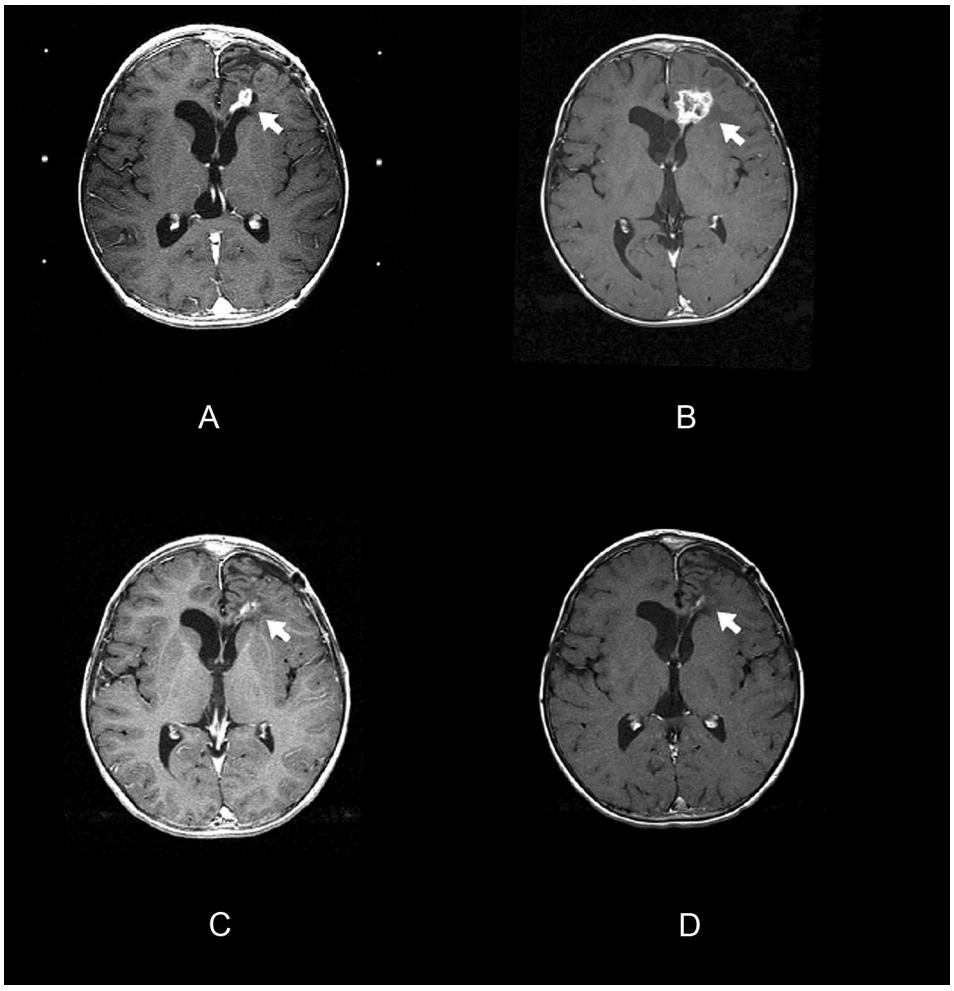

Fig. 3. Postcontrast T1-weighted images of a 6-year-old boy on the day of gamma knife radiosurgery and at 6 months, 9 months, and 15 months after gamma knife radiosurgery. (A) On the date of radiosurgery, there was a small enhancing recurrent tumor in the left frontal near frontal horn (arrow). (B) Six months after radiosurgery, there was an increasing enhancing area with a central loss-enhancement portion of the treated tumor (arrow). (C) Nine months after radiosurgery, the enhancing area shrunk without additional treatment (arrow). (D) Fifteen months after radiosurgery, the enhancing lesion further decreased and was not easily observed in magnetic resonance imaging (arrow).

enlargement of a post-GKRS ependymoma lasts longer than 6 months, closer imaging follow-up or another adjuvant treatment might be considered as timely management avenues.

In the current series, the lesions of pseudoprogression not only showed marginal or irregular ring enhancement with fuzzy margins similar to the post radiation changes, but also showed persistent enhancement or new enhancement, mimicking true progression. The pathological examination of one pseudoprogression case showed radiation-induced vascular changes, from which we might infer that radiation-induced vascular changes is one of the microscopic mechanisms in pseudoprogression. Furthermore, all the cases except one (a grade II ependymoma) in the current series received pre-GKRS conventional radiation therapy. The accumulated irradiation dose, instead of concomitant temozolomide or chemotherapy, might have been a factor triggering the pseudoprogression in the current study. Diffusion weighted imaging was also helpful in differentiating pseudoprogression from true progression. Higher mean post-GKRS ADC values of enhancing lesions and higher post-GKRS to pre-GKRS ADC ratios in pseudoprogression than true progression probably reflects the lower cellularity and/or increased vasogenic edema caused by radiation-induced vascular changes in pseudoprogression.

Although achieving tumor regression manifested by neuroimaging is the treatment goal, tumor enlargement does not always indicate treatment failure. In our study, the local tumor control rate in the first 2 years in patients who had pseudoprogression was similar to those who had a stable or decreased tumor size; both groups had better tumor control rate than those with true progression. In patients with initial tumor enlargement observed on MRI within the first post-GKRS 12 months, the management of choice might be *wait-and-see* with a closer imaging follow-up prior to true progression is suggested by continuous and progressive enlargement.

Table 1
Predictors of pseudoprogression and true progression.

Variable	Pseudoprogression	True progression	*p*
Age (y)	17	14	0.708
Prior RT dose (cGy)	5320	4754	0.572
Time interval between RT and GKRS (mo)	57.3	60.9	0.785
Mean GKRS dose (Gy)	20.9	16.7	0.122
GKRS volume (mL)	2.22	4.58	0.554
Onset of tumor enlargement (mo)	7.9	4.9	0.07
Tumor location			
Supratentorial	2	3	0.2767
Infratentorial	5	2	
New enhancement post GKRS			
Present	3	3	0.92
Absent	4	2	
ADC values when enlarged (10^3 mm^2/s), mean ± SD	1.41 ± 0.23	0.85 ± 0.06	0.002*
ADC ratio (post-GKRS/pre-GKRS), mean ± SD	1.15 ± 0.11	0.92 ± 0.02	0.005*
Follow up after 6 mo			
Enlargement	1	5	0.03*
Decrease in size	6	0	

* Statistically significant ($p < 0.05$).
ADC = apparent diffusion coefficient; GKRS = gamma knife radiosurgery; MRI = magnetic resonance imaging; RT = radiation therapy; SD = standard deviation.

The retrospective nature of this study had several limitations. First, the treatment modalities and chemotherapy regimen were heterogeneous. Second, we did not incorporate advanced MRI techniques, such as MRI spectroscopy and MRI perfusion, into the studying imaging protocol. Third, only two patients had surgical and pathological confirmation of their post-GKRS recurrent tumors. Thus, a comprehensive pathophysiological explanation of the tumor response to GKRS is not achievable.

In conclusion, dynamic tumor volume changes in recurrent ependymomas or anaplastic ependymomas are observed in serial of post-GKRS MRI follow-up. Pseudoprogression, with transient initial tumor enlargement, mostly regresses within 6 months, and occurs in 58% of tumors with initial post-GKRS tumor enlargement. Low-grade ependymoma (WHO grade II) might require more time to regress. ADC values are simple and readily available techniques that can help to differentiate pseudoprogression from true progression after GKRS. Serial follow-up MRI is also beneficial in differentiation by post-GKRS tumor enlargement resolved in 6 months indicating pseudoprogression.

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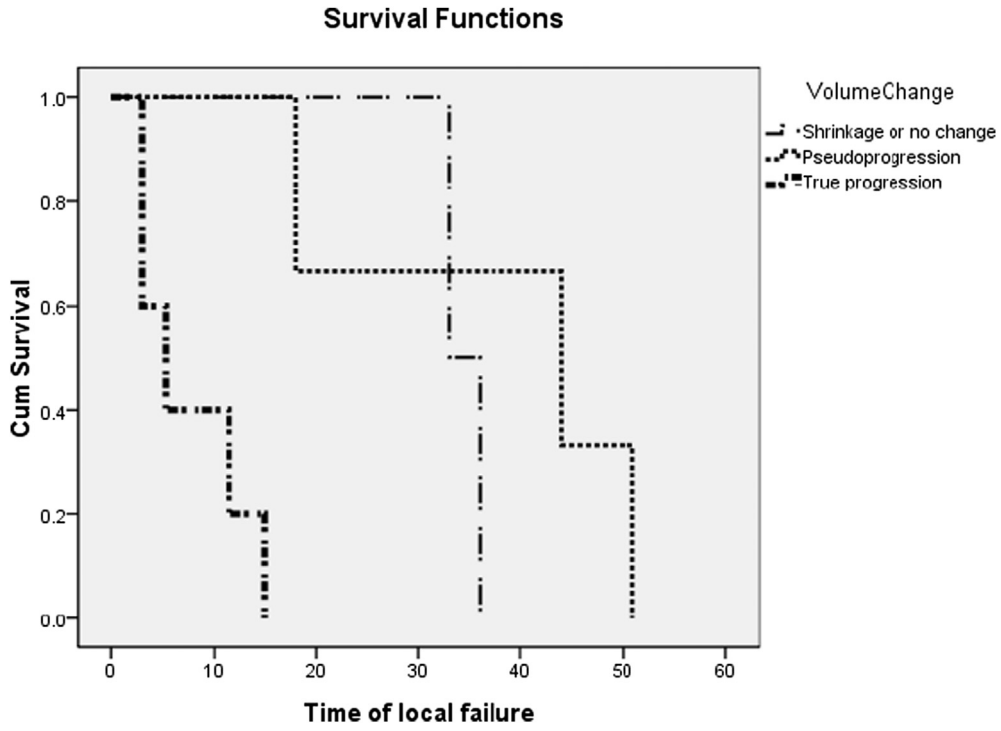

Fig. 4. Kaplan–Meier curve of local tumor control. There were no significant differences in the local tumor control rate in first 2 years between patients who had pseudoprogression and those who had a stable or decreased tumor size ($p = 0.364$), whereas those who had true progression exhibited worse local tumor control ($p = 0.006$).

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