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ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 292–298

www.jcma-online.com

Original Article

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

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Received May 26, 2015; accepted October 13, 2015

**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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http://dx.doi.org/10.1016/j.jcma.2015.10.005

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