



Stereotactic Gamma Knife Surgery in the Management of Deep-Seated Pilocytic Astrocytomas: Long-Term Outcomes

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Abstract

Background: While complete surgical extirpation of pilocytic astrocytoma is usually curative, however when these tumors are deeply-seated gross total resection is ill-advised because of the high morbidities.

Objective: This study aims to evaluate the outcomes of gamma knife surgery in the management of symptomatic residual and recurrent deep-seated pilocytic astrocytomas.

Patients and Methods: This study included 14 consecutive patients with residual or recurrent solid and mixed PAs treated at the International Medical Center-Gamma knife center- Cairo Egypt, from 2003 till the end of 2017. The mean follow-up period was 60 months (range 24 to 180). Five patients had solid tumors only and 9 had mixed tumor types. The mean treated solid tumor or mural nodule volume is 2 cc, the mean peripheral prescription dose is 11.7 Gy and the mean maximum dose is 28 Gy.

Results: At last follow-up, 11 patients (78.6%) achieved tumor growth control and three patients reported having a progression of the whole tumor. The actuarial tumor Progression-Free Survival (PFS) at 2, 3, 5 and 10 years is 76.9%, 72.7%, 71%, and 60% respectively. The tumor control rate with a mixed type tumor is 77.7% and is 80% for solid tumor type.

Conclusion: This series demonstrates and supports the favorable GKS long-term outcomes in the management of symptomatic critically located deep-seated residual and recurrent PAs <3 cm in maximum diameters after targeting the solid tumor or mural nodule rather than the entire cystic, allowing for better coverage of the nidus with the maximum radiation dose and consequently tumor growth control.

Keywords: Astrocytoma; Gamma knife surgery; Pilocytic astrocytoma; Stereotactic radiosurgery

Abbreviations

GKS: Gamma Knife surgery; Pas: Pilocytic Astrocytoma; SRS: Stereotactic Radiosurgery; WHO: World Health Organization

Introduction

Pilocytic Astrocytomas (PAs) are relatively uncommon generally considered benign low-grade gliomas, histological types of grade I astrocytomas (WHO classification) typically arise from within the cerebellum, brainstem, and hypothalamus in children and young adults. Unlike high-grade gliomas, pilocytic astrocytomas do not directly invade adjacent neural tissue rather they can grow to considerable size before a diagnosis is made. PAs represent between 1% and 5% of all intracranial tumors and 1.7% to 7% of glial tumors, in children PAs represent 70% of cerebellar astrocytomas [1-6].

Pilocytic astrocytomas usually are well-circumscribed tumors that may be cystic, solid, or a mixture of both components, the cystic mixed form is found in more than 75% of patients. Frequently mixed tumor type consists of a mural nodule at the edges of a cystic mass. These tumors are generally slow-growing and may stabilize for prolonged periods with or without intervention. Radiographically PAs typically contain a large cystic component although they can present as solid or a mixture of cystic and solid components that usually enhanced with contrast [5-12].

Pilocytic astrocytomas are potentially curable by complete surgical extirpation and have been associated with 10-year survival rates of 90% in children and 63% to 83% in adults. Nevertheless,

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complete resection is not always feasible and ill-advised when deeply seated in a critical location (e.g. hypothalamus, brain stem). In these cases, surgical options are limited to partial resection or biopsy. After this initial approach, patients are observed and may offer adjuvant radiotherapy or chemotherapy for residual and recurrence [1,10-16]. Conventional radiation therapy with relatively wide target volumes has been used but it is undesirable in children because of its possible side effects on cognition and the increased risk for the development of late secondary malignancy [3,11,13,17-20].

Regarding the cyst wall in mixed type pilocytic astrocytoma, until now no systematic histopathological examinations of the cyst walls have been reported in correlation with MRI images, intraoperative appearance and postoperative clinical and MRI follow-up. Beni-Adani et al. [14] presented 3 patients with mixed type pilocytic astrocytoma with brightly enhanced cyst walls on MRI, only radical removal of the mural nodule was performed and the cyst wall was biopsied and examined histologically that showed no tumor cells.

Palm et al. [9] in an analysis of the surgical results obtained for 51 cystic pilocytic astrocytomas with solid components concluded that total extirpation of the solid part of the tumor is usually associated with the best outcome and low rate of recurrences whether or not the cyst wall is completely removed. On the other hand, partial excision of the nodule correlated with poor results and often resulted in multiple operations and recurrences. Intra-operatively the cyst wall looks transparent and when examined histologically it showed no tumor cells although it appeared enhanced in post contrast MRI [14].

While stereotactic gamma knife surgery has been demonstrated as an effective local therapy for patients with pilocytic astrocytoma, published data on this topic, especially for critically deep-seated, tumors remained limited no randomized controlled trial comparing therapies for these patients has been done and few prospective data is available owing to the disease and location rarity [1,2,11,17,20-22].

Objective

Our primary objective is to evaluate long-term outcomes of stereotactic gamma knife surgery in the management of symptomatic residual and recurrent deep-seated pilocytic astrocytomas targeting only the solid mural nodule. A retrospective analysis of clinical and radiographic outcomes was conducted and reported for 14 consecutive treated patients with GKS in our center for such a rare tumor in a critical deep location.

Patients and Methods

Patient's population

This study included 14 consecutive cohort patients with histologically verified symptomatic critically deep-seated post-operative residual and recurrent PAs who underwent GKS targeting the solid tumor or the mural nodule in mixed type at the International Medical Center- Gamma knife center- Cairo Egypt, from 2003 till the end of 2017. There were 7 females and 7 males with a mean age of 16.5 years (range 6 to 25 years). The mean follow-up was 60 months (range 24 to 180). All studied patients deemed ineligible for total resection because of the deep-seated tumor location instead underwent either stereotactic or open biopsy and cyst aspiration or partial tumor removal. One of the early treated patients failed to continue follow-up and was excluded from the study.

Although the GKS target in all our studied cases was the solid part of the tumor or the mural nodule, the maximum diameters of

the whole tumor including the cyst was <3 cm. Larger solid tumor or larger mixed tumor type with large cyst needed other options of treatment including microsurgery, cyst aspiration or even fractionated radiotherapy.

Ten patients were treated with GKS as part of their initial tumor management for residual symptomatic untestable tumor after stereotactic or open biopsy with cyst aspiration; the remaining 4 were treated at the time of tumor recurrence after initial partial tumor removal. Five patients had solid PAs type and 9 had mixed tumor type (cyst and mural solid nodule components). Clinical characteristics were collected including patient age, gender, Karnofsky Performance Status (KPS), and previous therapies (i.e. surgery, chemotherapy, and or fractionated external beam radiotherapy). Pre-GKS two patients had Ventriculoperitoneal CSF shunting.

Various common GKS parameters were recorded including, peripheral prescription dose in Gy, isodose line %, maximum dose in Gy for the detected solid tumor or mural nodule, percentage of coverage %, tumor characters including location, volume, and the presence of cystic features also reported and summarized in Table 1, 2.

Statistical analysis

Patient, tumor, and GKS characteristics were collected and reported using common arithmetic analyses. Local Control (LC), Overall Survival (OS) and tumor Progression-Free Survival (PFS) was performed utilizing commercially available statistical software (NCSS, LLC 2019.exe, and PASS).

Gamma knife procedure

Elekta Leksell Gamma Knife (Models B and 4C; Elekta AB) and Gamma Plan Version 10.1 were used in this study for treatment. The standard Leksell G-stereotactic head frame is applied after local anesthesia. Target localization was obtained using high-resolution MRI (1.5-3T), obtaining T1, T2, sequences with contrast at 1.2 mm slice thickness on zero angles without slices gap. Gamma knife Plans consisted of a mixture of shots using usually the 4 and the 8 mm helmets collimator, focusing the maximum GKS radiation dose on the solid part of the tumor or the mural nodule in mixed PAs obtaining maximum radiation conformity while sparing the cyst. Treatment was technically feasible for all cases. After GKS treatment completion the stereotactic frame removed and all patients discharged on the same day. The mean treated tumor volume (solid part) upon initial GKS was 2 cc (range 0.35 cc to 5.3 cc), the mean peripheral prescription dose given to identified solid part of the tumor was 11.7 Gy (range 10 Gy to 12 Gy), the mean isodose line was 43.3% (range 35% to 60%), the mean tumor coverage was 98% (range 90% to 100%) and the mean maximum dose was 28 Gy which was focused mainly and totally on the solid part of the tumor (range 16.7 Gy to 34.4 Gy) (Table 2).

Clinical and radiographic follow up

Patients were evaluated clinically and with imaging using contrast MRI every 6 months in the first year then annually for 5 years, then after every two years or whenever clinically indicated. Some of those early treated patients since 8 to 10 years preferred phone call evaluation by gamma knife physician rather than attendance as long; they were clinically improved or stable. All patients had a minimum of 24 months follow-up with a mean follow-up of 60 months (range 24 to 180). The standard GKS response classification was used to assess treatment outcomes either Tumor growth Control = TC

Table 1: Clinical and tumor characteristics of the studied 14 patients with residual and recurrent deep-seated pilocytic astrocytoma treated with stereotactic Gamma knife surgery.

Case No	Sex	Age	Tumor location	Tumor characters	Presentation	KPS	Pre-GKS* surgeries	Follow up period-mos	Final outcome
1	F	11	Left Thalamic+ Basal ganglion	MIXED*	Right hemip*	90	Stereotactic Biopsy& cyst aspiration	180	Alive
2	F	19	Brain stem Pontomedullary	MIXED*	Vomiting+ Ataxia	80	Stereotactic Biopsy +cyst aspiration	156	Alive
3	F	21	Optic nerve+ hypothalamus	SOLID	Fit+ Visual Def*+DI*	80	Open Biopsy	22	Dead
4	M	20	Cerebellar peduncle	SOLID	Vomiting+ Ataxia	90	Part.R*+VP*+ Fractionated radiotherapy	132	Alive
5	F	19	Right thalamic&brain stem involvement	MIXED*	H*+Left hemip*	80	Stereotactic Biopsy& cyst aspiration	16	Dead
6	M	18	Left Thalamic+brain stem involvement	MIXED*	Visual Def*+Vomiting +Ataxia	80	Stereotactic Biopsy& cyst aspiration	84	Alive
7	F	19	Left Thalamic+ Basal ganglion	MIXED*	Visual Def*+Right hemip*	90	Stereotactic Biopsy& cyst aspiration	60	Alive
8	M	19	Cerebellar peduncle	SOLID	Ataxia+VisualDef *	90	Part. R*+VP*	48	Alive
9	F	9	Diencephalic+brain stem involvement	MIXED*	H+ Visual Def*+Right hemip*	90	Part. R*	20	Alive
10	M	6	Mid brain	SOLID	Vomiting+Left hemip*	90	Stereotactic Biopsy& cyst aspiration- chemotherapy	36	Alive
11	M	8	Cerebellar peduncle	MIXED*	Headache+ Ataxia	90	Part. R*	36	Alive
12	M	25	left thalamic +Basal ganglion	MIXED*	Right hemip*	90	Stereotactic Biopsy& cyst aspiration	24	Alive
13	F	19	Brain stem+Tectum +Splenum	SOLID	H+ + Visual Def*+ Ataxia	90	Stereotactic Biopsy& cyst aspiration	24	Alive
14	M	20	Left thalamic+ Diencephalon	MIXED*	H+ + Visual Def*+ Right hemip*	90	Stereotactic Biopsy& cyst aspiration	24	Alive

DI*: Diabetes insipidus; GKS*: Gamma Knife Surgery; hemip*: Hemiparesis; H*: Headache; KPS: Karnofsky Scoring; Mixed*: Cystic and Mural Mural Nodule; mos*: Months; Part R*: Partial Tumor Removal; VP*: Ventriculoperitoneal Shunt; Visual D*: Visual defect

Table 2: Stereotactic Gamma Knife Surgery (GKS) treatment parameters for 14 patients with deep-seated pilocytic astrocytoma.

Case No	Treated Tumor volume (Solid part or mural nodule) cc*	Prescription dose Gy	Isodose curve %	Coverage%	Maximum dose Gy	Post-GKS* Response	Time till TC*or LTC* post GKS*- mos*	Post-GKS* treatment
1	0.439	12	50	100	24	TC* Decreased	180	-
2	1.5	12	50	99	24	TC* Decreased	156	-
3	4.2	12	60	90	20	LTC* Progresses	22	Chemotherapy +Fractionated radiotherapy
4	1.2	12	35	100	34.3	TC* Decreased	132	-
5	4.4	12	35	95	34.4	LTC* Progresses	16	Cyst aspiration +Fractionated radiotherapy
6	0.5	10	35	99	28.6	TC* Decreased	84	-
7	2.5	12	35	98	34.3	TC* Stable	60	-
8	0.778	12	35	99	34.3	TC* Stable	48	-
9	5.3	12	35	97	34.3	LTC* Progresses	20	Microsurgery
10	0.826	10	50	99	20	TC* Decreased	36	-
11	1.78	12	48	98	25	TC Stable	36	-
12	1.97	12	38	98	31.7	TC Stable	24	-
13	1.25	12	50	99	24	TC* Decreased	24	-
14	0.352	12	50	100	24	TC* Decreased	24	-

cc*: Cubic Centimeter; GKS*: Gamma Knife Surgery; TL*: Tumor Growth Control; LTC*: Loss Tumor Growth Control; mos*: months

(decreased or stable in size) and Loss Tumor growth Control = LTC (tumor progression in size solid or cystic component).

Results

The most common tumor location in our study was the thalamus and/or basal ganglion in 6 patients, brain stem in 4, cerebellar peduncle in 3, hypothalamus and optic chiasm in one patient.

The six thalamic and basal ganglion PAs were mixed type (Cyst

and mural nodule), two of the brain-stem tumors were mixed type and 2 were just solid tumors. One of the treated recurrent cerebellar peduncle tumors was mixed type and two were the solid type. The treated residual hypothalamic tumor was a solid tumor type.

Clinical and local tumor control

At last follow-up 11 patients (78.6%) achieved Tumor growth Control (TC), 7 of them had a different degree of tumor size regression, and the remaining 4 had a local stable tumor size. Different degree of

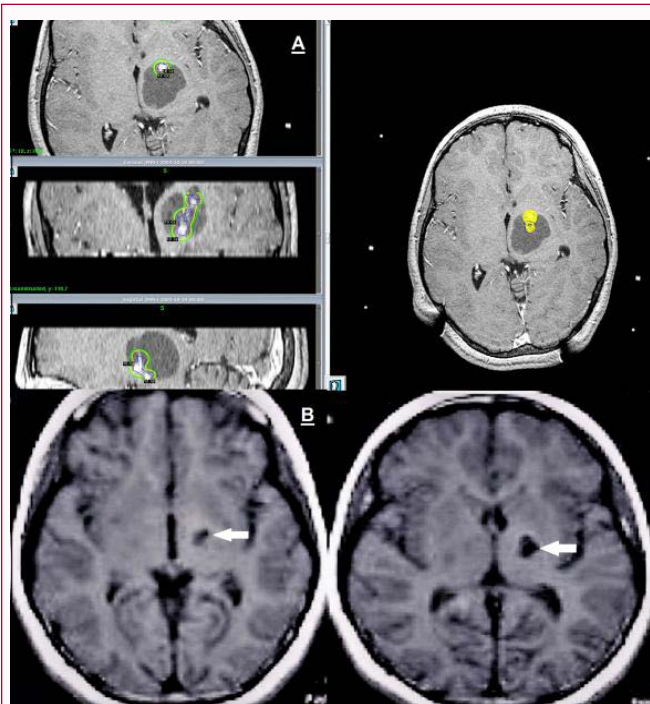


Figure 1: (A) Stereotactic 3D- T1-weighted contrast enhanced MRI Gamma plan of left thalamic mixed pilocytic astrocytoma in 11 year old girl with 0.44 cc volume mural nodule targeted with GKS with 12 Gy at 50% isodose line with 24 Gy maximum dose. (B) 180 months post GKS with axial MRI with contrast showed a marked decrease in the whole tumor (cyst and mural nodule). The patient showed significant improving of her neurological status.

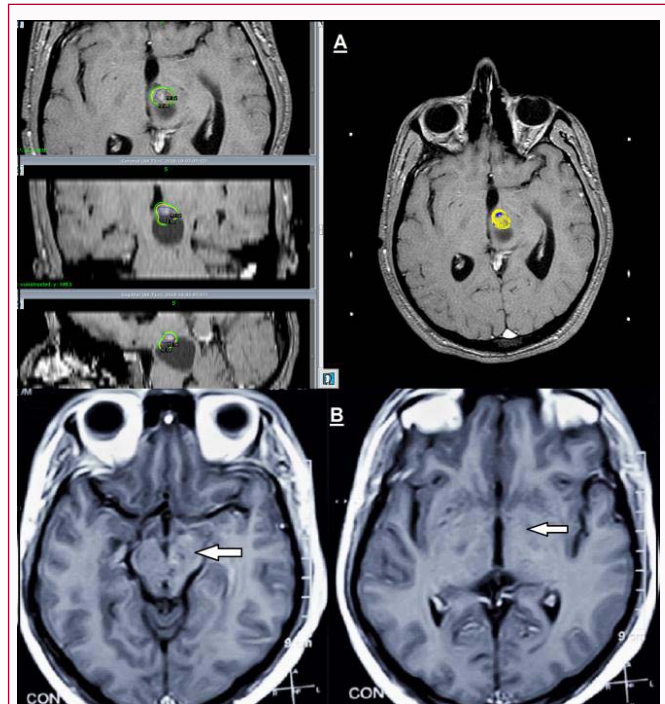


Figure 2: (A) Stereotactic 3D- T1-weighted contrast enhanced MRI Gamma plan of left thalamic and brain stem mixed pilocytic astrocytoma in 18 year old male with 0.5 cc volume mural nodule targeted with GKS with 12 Gy at 50% isodose line with 28.6 Gy maximum dose. (B) 84 months post GKS with axial MRI with contrast revealing decrease in the whole tumor volume (cyst and mural nodule) and clinically the patient is improved.

clinical improvement was reported in those achieved TC, 5 of them had mixed tumor and 2 had solid tumors, while the other 4 patients were clinically stable. Illustrative cases demonstrated in Figures 1-3.

Most of those achieved tumor reduction and significant cyst contraction occurred within 12 to 24 months post-treatment. At the time of the final assessment, 12 patients were alive and two patients had died 22 and 16 months post-GKS.

Three patients (21.4%) were reported having radiographic progression of their treated tumor with clinical deterioration during the follow-up, the mean treated tumor volume in these 3 patients was 4.6 cc (range 4.2 cc to 5.3 cc). Case No 3 female patient 21 years old with 4.2 cc solid residual hypothalamic and optic chiasm PAs developed tumor progression and deterioration 22 months post-treatment she has retreated with chemotherapy and fractionated radiotherapy. Case No 5 female 18 years old had 4.4 cc mural nodule of residual right thalamic mixed PAs with brain stem involvement, tumor progression and clinical deterioration occurred 16 months post GKS; she has retreated with cyst aspiration and fractionated radiotherapy. Case No 9, nine years old girl with recurrent left thalamic mixed PAs and brain stem involvement with treated mural nodule volume of 5.3 cc, she developed tumor progression and clinical deterioration 20 months post-GKS the patient has been re-operated micro-surgically and received fractionated radiotherapy (Table 1, 2).

Tumour characters and growth control

Seven of the treated 9 patients with mixed PAs type achieved tumor growth control, 5 of them had cyst reduction and 2 had stable tumor size. Four of the 5 patients with solid tumor type achieved

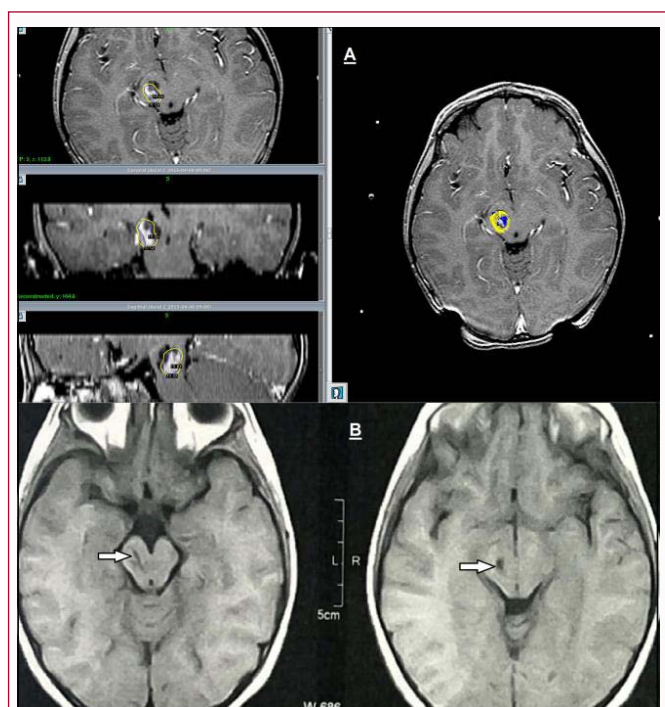


Figure 3: (A) Stereotactic 3D- T1-weighted contrast enhanced MRI in Gamma plan of 0.826 cc right mid-brain post stereotactic residual pilocytic astrocytoma in 6 year old boy treated with GKS with 10 Gy at 50% isodose line with 20 Gy maximum dose. (B) 36 months post GKS axial MRI with contrast showed marked decrease in tumor size with stable clinical status.

tumor growth control 2 of them had tumor reduction and 2 were stable size.

In this series the reported survival rate post-GKS at 2, 3, 5, 10 years was 81.8%, 71.4%, 66.6%, and 60% respectively. The overall tumor control rate was 78.6% and the actuarial tumor progression-free survival (free from progression) at 2, 3, 5 and 10 years was 76.9%, 72.7%, 71%, and 60% respectively.

No patient developed an Adverse Radiation Effect (ARE) after GKS till the last follow-up.

Discussion

The outcomes of GKS in the treatment of histologically verified critically located deep-seated PAs infrequently reported in the literature per se especially with the mixed PAs. Most of the reported surgical results of mixed type PAs strongly agreed on evident better results obtained when the mural nodule is removed even without removing the cyst wall. Partial removal of the mural nodule in mixed PAs usually associated with a higher recurrence rate and cyst recollection. Histologically the cyst wall in cystic PAs does not prove yet to have any active tumor cell [1,9,10,14].

Hafez [17], illustrated significant cyst and tumor volume reduction 12 months post-GKS targeting the mural nodule nidus in two reported critically deep-seated residual mixed type PAs.

In our series the target of GKS among treated the patients with mixed tumor type was the mural nodule sparing the cyst concentrated the given maximum radiation dose within the solid mural nodule as expected to be the source of cyst fluid formation and tumor growth.

Boethius et al. [2], reported 19 PAs patients who underwent gamma knife surgery for PAs using a margin dose of 10 Gy to 12 Gy, resulted in 100% tumor control at a mean radiological follow-up of 5.9 years, tumor regression was noted in 85% of patients, cystic development occurred in 10.5% of patients.

Kano et al. [5], in a series over 50 patients underwent GKS for postoperative residual or recurrent pilocytic astrocytoma, 19 patients had their tumors deeply-seated and 31 had a tumor in none eloquent area, 31 patients of the total had a solid tumor and 19 has mixed tumor type. The authors reported a 3-, 5 year progression-free survival of 70.7% and 53.9% in critical deep-seated tumors, and a 3-, 5 year progression-free survival of 90.2%, and 83.8% respectively with tumors in none critical location. Also reported a 3-, 5- year progression-free survival of 100% and 94.40% in the 31 patients with solid tumors type and a 3-, 5 year progression-free survival of 53.1 and 21.3%, respectively in 19 patients with mixed tumor, with better prognosis with solid tumor type [5,6].

The results obtained in our series confirm GKS as an effective modality in the management of symptomatic deep-seated unresectable residual or recurrent pilocytic astrocytoma after targeting the solid part of the tumor with an overall local control rate of 78.6%. The overall survival rate was 85.7 and the survival rate at 2, 3, 5, 10 years was 81.8%, 71.4%, 66.6%, and 60% respectively.

As reported in most of the series [1,2,5-8], a small target volume was significantly associated with better progression-free survival. We reported a mean tumor volume of 1.4 cc (range 0.35 cc to 2.5 cc) in 11 patients who achieved tumor growth control and mean tumor volume of 4.6 cc (range 4.2 cc to 5.3 cc) in the 3 patients who lost tumor growth control post-GKS.

The Planning Target Volume (PTV) reported in Kano et al. [5] series and others authors [1,2,4,8,11,14], is the whole PAs tumor volume included the solid and cystic part, consequently the maximum radiation dose was not concentrated on the mural nodule which expected to be the source of the fluid formation.

In our series, the Progression-Free Survival (PFS) for mixed tumor type at 2, 5 and 10 years is 75%, 75%, and 50% and for solid tumor type is 80%, 66.7% and 50% respectively. The mean maximum radiation dose is 28 Gy (range 10 Gy to 12 Gy) which is concentrated on the solid tumor or the mural nodule. These probably explained the better prognosis we obtained in mixed tumor type where 7 patients of the treated mixed tumor type achieved tumor control at last follow-up 5 of them had marked tumor and cyst reduction. This finding is potentially due to targeting only the mural nodule rather than the entire cystic component, which allows for better coverage of the nidus with the maximum radiation dose.

Resembling what confirmed with surgical results of the low rate of recurrences and cyst recollection when solid mural nodule extirpation is achieved in mixed PAs type [1,7,9,14]. In our study the concentration of GKS maximum radiation dose within mural nodule in mixed PAs was associated with a high rate of tumor growth control and evident decrease in whole tumor volume.

Strengthens and Limitations

The relative homogeneity of the studied 14 consecutive patients treated with GKS targeting the exciting solid components of residual or recurrent critically deep-seated pilocytic astrocytoma strengthens the study in the face of somehow limited study size of these rare tumors. This retrospective study represents a limitation. Further longer follow-up and accumulation of cases are hence still required.

Conclusion

This series demonstrates and supports the favorable GKS long-term outcomes in the management of symptomatic residual and recurrent deep-seated Pas <3 cm in maximum diameters when targeting the solid tumor or mural nodule. The overall tumor control rate is 78.6% and the overall survival rate is 85.7%. The tumor control rate with a mixed type tumor is 77.7% and is 80% for solid tumor type. The favorable results obtained in this series with GKS for mixed tumor PAs are potentially due to targeting the mural nodule rather than the entire cystic component allowing for better coverage of the nidus and consequently tumor growth control. Longer follow-up and larger series will serve to define the optimal treatment strategies and GKS role in the management of PAs seated in deep critical locations.

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