

Gamma Knife Surgery in the Management of Residual Critical Deep-Seated Partially Cystic Pilocytic Astrocytomas

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ABSTRACT

Objective: Complete surgical extirpation of pilocytic astrocytoma is usually curative, however when these tumors are critical deeply-seated gross total resection is usually not feasible and ill-advised because of the high morbidities. The objective of this study is to evaluate the outcomes of Gamma Knife Surgery in the management of critical deep-seated postoperative residual partially cystic pilocytic astrocytoma < 3cm in maximum diameter targeting the solid mural nodule.

Patients and methods: This study included 9 consecutive patients 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. The mean treated solid mural nodule volume is 2 cc, the mean peripheral prescription dose is 11.7Gy and the mean maximum dose is 29.4Gy.

Results: At last follow-up, 7 patients (78%) have tumor growth control. Two patients were reported having progression of treated whole tumor. The overall actuarial tumor progression-free survival (free from progression) at 1, 3, 5 and 8 years was 78%, 72.7%, 71% and 60% respectively.

Conclusion: This study demonstrates favorable outcome of GKS in the management of residual critically deep-seated partially cystic PAs <3cm in maximum diameters when targeting the solid mural nodule allowing coverage of the nidus with the maximum GKS radiation dose that resulting in significant tumor control and cyst reduction.

ABBREVIATIONS

GKS: Gamma Knife Surgery; PAs: Pilocytic Astrocytomas; SRS: Stereotactic Radiosurgery; WHO: World Health Organization

BACKGROUND

Pilocytic Astrocytomas (PAs) are relatively uncommon low-grade gliomas that typically arise from within the cerebellum, brainstem, and hypothalamus of young patients. 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. Pilocytic Astrocytomas (PAs) are histological types of grade I astrocytomas (WHO classification) [1-3].

Although Pilocytic astrocytomas represent between 1% and 5% of all intracranial tumors and 1.7%-7% of glial tumors, they are common brain tumors in children representing 70%-80% of cerebellar astrocytomas [1,4-6].

PAs 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 tumor [8,9]. While complete surgical extirpation is usually curative, the location and extent of pilocytic astrocytomas near the brain stem or optic structures commonly makes gross total resection of these tumors ill-advised because of expected neurologic deficits following resection in these areas [5-12].

Pilocytic astrocytomas are potentially curable by surgery and have been associated with 10-year survival rates of 90% in children and 63-83% in adults. Nevertheless, complete resection is not always feasible depending on the location of the tumor (e.g. hypothalamus, brain stem). In these cases, surgical options are limited to partial resection or biopsy. After this initial approach, patients are observed or offered adjuvant radiotherapy or chemotherapy for residual or recurrence [1,10,13-16].

Conventional radiation therapy for partially cystic PAs with relatively wide target volumes has been used but is undesirable in children because of its possible side effects on cognition and the increased risk for the development of a secondary malignancy [3,13,17-19]. Stereotactic gamma knife surgery minimizes these potential radiation-related side effects by targeting the tumor precisely through focused radiation beams. However, no randomized controlled trial comparing therapies for these patients has been done, and few prospective data is available [1,2,11,20].

Regarding the cyst wall in cystic in mixed type pilocytic astrocytoma, until now no systematic histopathological examinations of cyst walls have been reported in correlation with MRI images, intraoperative appearance and postoperative clinical and MRI follow-up. Beni-Adani et al 2000, presented 3 patients with mixed type pilocytic astrocytoma with brightly enhanced cyst walls on MRI. Because of the tumor benign nature, and the transparent appearance of the cyst wall intraoperatively it was biopsied but not resected, and only radical removal of the mural nodule was performed. Separate specimens taken from the cyst wall showed no tumor cells [14].

Palm et al; 1985 in an analysis of the surgical results obtained for 51 partially cystic pilocytic astrocytomas with solid

components concluded that total extirpation of the solid mural part 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 especially the cyst in mixed tumor type [9].

Hafez R 2007, reported a significant reduction of the cyst volume with tumor growth control for two postoperative residual mixed type critically located pilocytic astrocytoma patients post GKS targeting only the detected mural nodules solid part and sparing the cyst [17].

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 deep-seated critically located pilocytic astrocytoma remained limited owing to the disease and location rarity [1,4-6,13].

OBJECTIVE

The main objective of this study is to evaluate the outcomes and efficacy of Gamma Knife Surgery in the management of critical deep-seated post-operative residual partially cystic pilocytic astrocytoma targeting the mural nodule of the tumor. A retrospective analysis of clinical and radiographic outcomes was conducted and reported for 9 consecutive PAs patients treated with GKS in our center for such a rare tumor residual in critical deep-seated location.

MATERIALS AND METHODS

Patient's population

This study included 9 consecutive cohort patients with critically deep-seated histologically verified residual partially cystic PAs underwent GKS targeting the solid mural nodule and sparing the cyst, treated at the International Medical Center- Gamma knife center- Cairo Egypt, from 2003 till the end of 2017. There were 5 females and 4 males with mean age of 16.4 years (range 8-25years). The mean follow-up period was 60 months (12-180mos).

All studied patients had deep-seated tumors deemed ineligible for total resection instead underwent either stereotactic biopsy with cyst evacuation (7 patients) or partial tumor removal in (2 patients). GKS used in all treated cases as part of their initial treatment for post-operative tumor residual.

The maximum diameters of the whole tumor including the cyst was <3cm. The GKS main target in all our studied cases was the solid mural nodule sparing the cyst from radiation.

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). At the time of gamma knife treatment tumor characteristics were collected including location, volume, and the presence of cystic features. Various common Gamma knife surgery 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% (Table1&2).

Pre-GKS two patients had ventriculoperitoneal CSF shunt and one had Omiya reservoir. Larger partially cystic PAs >3cm in maximum diameter with large cyst usually advised to undergo microsurgery, stereotactic or open biopsy with cyst aspiration.

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 angle without slices gap. It was possible to identify the mural nodule or nodules in all cases usually at the edges of the cyst as solid enhanced part in T1 with contrast sequences and iso or hypointense in T2 sequences. Gamma knife Plans consisted of a mixture of shots using usually 4 and the 8mm helmets collimator depends on tumor volume and the radiation conformity needed. Treatment was technically feasible for all cases. After GKS treatment completion the stereotactic frame removed and all patients discharged in the same day.

Table 1: Clinical and tumor characteristics of the 9 patients for residual deep-seated mixed pilocytic astrocytomas treated with stereotactic Gamma knife surgery.at the IMC-Cairo-Egypt, between 2003-2017 targeting the solid mural nodule part of the tumor.

Case No	Sex	Age	Tumor location	Tumor characters	Presentation	KPS	Pre-GKS* surgeries	Time till last follow up / 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	19	Right thalamic& brain stem involvement	MIXED*	H*+Left hemip*	80	Stereotactic Biopsy& cyst aspiration	16	Dead
4	M	18	Left Thalamic+ brain stem involvement	MIXED*	Visual Def*+ Vomiting +Ataxia	80	Stereotactic Biopsy& cyst aspiration	84	Alive
5	F	19	Left Thalamic+ Basal ganglion	MIXED*	Visual Def*+ Right hemip*	90	Stereotactic Biopsy& cyst aspiration	60	Alive
6	F	9	Diencephalic+ brain stem involvement	MIXED*	H+ Visual Def* +Right heimp*	90	Part. R*	20	Alive
7	M	8	Cerebellar peduncle	MIXED*	Headache+ Ataxia	90	Part. R*	36	Alive
8	M	25	left thalamic +Basal ganglion	MIXED*	Right hemip*	90	Stereotactic Biopsy& cyst aspiration	24	Alive
9	M	20	Left thalamic+ Diencephalon	MIXED*	H+ + Visual Def* + Right hemip*	90	Stereotactic Biopsy& cyst aspiration	12	Alive

Table 2: Stereotactic Gamma knife surgery (GKS) treatment parameters for 9 patients for residual deep-seated mixed pilocytic astrocytomas between 2003 and 2017 at the IMC-Cairo-Egypt, targeting the solid mural nodule part of the tumor.

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	4.4	12	35	95	34.4	LTC* Progresses	16	Cyst aspiration +Fractionated radiotherapy	
4	0.5	10	35	99	28.6	TC* Decreased	84	-	
5	2.5	12	35	98	34.3	TC* Stable	60	-	
6	5.3	12	35	97	34.3	LTC* Progresses	20	Microsurgery +Fractionated Radiotherapy	
7	1.78	12	48	98	25	TC Stable	36	-	
8	1.97	12	38	98	31.7	TC Stable	24	-	
9	0.352	12	50	100	24	TC* Decreased	12	-	

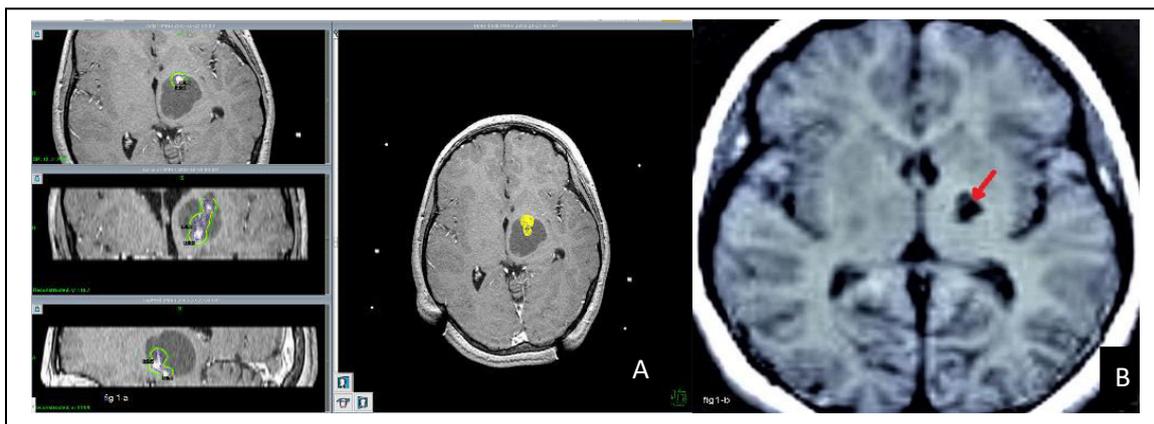


Figure 1: (a) Stereotactic 3D- T1-weighted contrast enhanced MRI Gamma plan of left thalamic partially cystic pilocytic astrocytoma in 11 year old girl with 0.44cc volume mural nodule targeted with GKS receiving 24Gy maximum radiation dose. (b) 180 months post GKS with axial MRI with contrast showed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

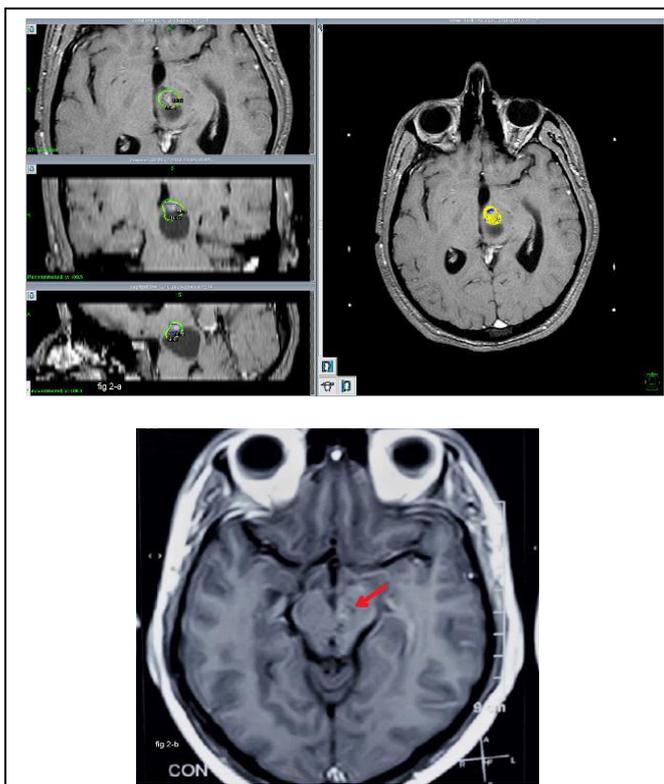


Figure 2: (a) Stereotactic 3D- T1-weighted contrast enhanced MRI Gamma plan of left thalamic and brain stem partially cystic pilocytic astrocytoma in 18-year-old male with 0.5cc volume mural nodule targeted with GKS receiving 28.6Gy maximum radiation dose.
(b) 84 months post GKS with axial MRI with contrast revealing decrease in the whole tumor volume (cyst and mural nodule) and clinically the patient is improved.

Clinical and radiographic follow up

Patients were evaluated clinically and radiologically with 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 8-10 years preferred phone call evaluation by gamma knife physician rather than attendance as long, they were clinically improved or stable, otherwise, MRI usually recommended. All patients had a minimum of 12 months follow-up with a mean follow-up of 60 months (range 12-180months). The standard GKS response classification was used to assess treatment outcomes either Tumor growth control =TC (decreased or stable in size) and Loss tumor growth control = LTC (tumor progression in size solid or cystic component). The mean Treated Tumor volume (solid mural nodule) upon initial GKS

was 2 cc (range 0.35–5.3 cc), the mean peripheral prescription dose given was 11.7Gy (range 10-12Gy), the mean isodose line was 42% (range 35%–50%), the mean tumor coverage was 98% (range 90–100%) and the mean maximum dose was 29.4Gy (range 24-34.4Gy) which was focused totally on the solid mural nodule part of treated residual mixed PAs.

RESULTS

Regarding the treated residual critical deep-seated partially cystic PAs tumor location, 6 were in the thalamus and/or basal ganglion, 2 were in the brain-stem and one in cerebellar peduncle tumor.

At last follow-up post-GKS, 7 patients (78%) achieved tumor control (TC), 4 of them had a different degree of tumor size and cyst regression, the remaining 3 had local stable tumor size. Different degrees of clinical improvement were reported in those achieved TC (Figure 1,2).

Two patients (22%) were reported having radiographic progression of their treated tumor with clinical deterioration during the follow-up period, the mean treated tumor volume in them was 4.9cc (range 4.4-5.3cc).

Most of those achieved tumor reduction with significant cyst contraction occurred within 12-24months post-treatment. At the time of final assessment, 8 (88%) patients were alive and one patient died 16 months post-GKS due to disease progression. No patient developed an adverse radiation effect (ARE) or suffered any other morbidity after GKS till the last follow-up.

In our series the reported overall survival rate at 1,3,5,8 years was 89%, 71.4%, 66.6%, and 60 % respectively. The overall actuarial tumor progression-free survival (free from progression) at 1, 3,5 and 8 years was 78%, 72.7%, 71% and 60% respectively.

DISCUSSION

The outcomes of GKS in treatment of histologically verified critically deep-seated partially cystic PAs infrequently reported in the literature per se. 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 [1,9,14-16,18].

Hafez R 2007, reported significant cyst and tumor volume reduction 12 months post-GKS for a detected mural nodule in two deep-seated residual mixed type PAs [17].

In this series the target of GKS for all treated patients with was the mural nodule sparing the cyst aiming to concentrate 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; 2002, reported 19 PAs patients who underwent gamma knife surgery for PAs using a margin dose of 10-12 Gy, resulted in 100% tumor control at a mean radiological follow-up of 5.9 years, tumor regression was noted in 85% of patients, cyst development occurred in 10.5% (2 patients). The author recommended stereotactic radiosurgery as a valuable option for newly diagnosed residual unresectable and recurrent critically located deep-seated PAs [2].

Kano et al; 2009, in a series over 50 patients underwent GKS for postoperative residual or recurrent pilocytic astrocytoma, 19 patients had their tumors deeply-seated (13 were in brain stem and 6 were in basal ganglion and thalamus) and 31 had tumor in none eloquent area, 31 patients of the total had solid tumor and 19 has mixed tumor type. The authors reported a 3-, 5year progression-free survival of 70.7% and 53.9 % for critical deep-seated tumors, and a 3-, 5year progression-free survival of 90.2%, and 83.8 % respectively for tumors in none critical location. Also reported a 3-, 5- year progression-free survival of 100% and 94.4 0% in 31 patients with solid tumors type and a 3-, 5year 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 Planning Target Volume (PTV) reported in kano et al; study and some others studies [1-5,8,11,14], where the whole solid and cystic part of the treated PAs tumor included within the radiation field, consequently, the maximum radiation dose was not concentrated on the mural nodule which expected to be the source of the fluid formation.

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 treated mural nodule volume of 1.3cc (range 0.38-2.5cc) in those who achieved tumor control post-GKS (7patients) and mean volume of 4.8cc

(range 4.4-5.3cc) for those lost tumor growth control (2 patients).

The mean maximum radiation dose in our series was 28Gy (range 10-12Gy) that is concentrated on the solid mural nodule and spared the cyst. These probably explained the better prognosis we obtained in mixed tumor type where 7 patients (78%) achieved tumor control at last follow-up, 4 of them had marked tumor regression and cyst reduction. The progression-free survival (PFS) or tumor free from progression at 1, 3,5 and 8 years was 78%, 72.7%, 71% and 60% respectively. The results obtained in our series confirm that GKS is an effective modality in the management of critically located deep-seated residual mixed pilocytic astrocytoma.

Resembling what confirmed with surgical results for partially cystic PAs in none critical location of the low rate of recurrences and cyst recollection after solid mural nodule extirpation is achieved [1,7,9,14,20], in this study the concentration of GKS maximum radiation dose at the mural nodule in is associated with a high rate of tumor growth control and evident decrease in whole tumor volume probably through stopping fluid formation and eventually cyst reduction.

STRENGTHENS AND LIMITATIONS

The relative homogeneity of the studied 9 consecutive patients with residual postoperative critically deep-seated partially cystic pilocytic astrocytoma treated with GKS targeting the exciting solid mural nodule 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 a favorable GKS outcome in the management of critically deep-seated residual partially cystic targeting the solid mural nodule. The overall tumor control rate is 78% and overall survival rate is 89% with mean follow up period of 60months. The favorable results obtained in this series is potentially due to targeting the mural nodule rather than the entire cystic component allowing for better coverage of the mural nodule with the maximum radiation dose and consequently tumor growth control with cyst reduction. Longer follow-up and larger series will serve to define the optimal treatment strategies for critically located deeply-seated residual or recurrent partially cystic mixed PAs.

RETROSPECTIVE STUDY

"For this type of retrospective study, formal consent or committee approval is not required; it does not contain any studies with human participants"

FUNDING

No funding was received for this research.

COMPETING INTERESTS

The authors declare that they have no competing interests, and certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. I declare that this is an original article and it was never published whole or in part or submitted elsewhere for review.

AUTHOR'S CONTRIBUTIONS

-Raef Farouk Ahmed Hafez, conceived, prepared, and reviewed the manuscript.

The author read and approved the manuscript.

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