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**Concise review of radiosurgery for contemporary management of pilocytic astrocytomas in children and adults**

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**Abstract**

Pilocytic astrocytoma (PA) may be seen in both adults and children as a distinct histologic and biologic subset of low grade glioma (LGG). Surgery is the principal treatment for management of PAs, however, selected patients may benefit from irradiation particularly in the setting of inoperability, incomplete resection, or recurrent disease. While conventionally fractionated radiation therapy (RT) has been traditionally utilized for radiotherapeutic management, stereotactic irradiation strategies have been introduced more recently to improve the toxicity profile of radiation delivery without compromising tumor control. PAs may be suitable for radiosurgical management due to their typical appearance as well circumscribed lesions. Focused and precise targeting of these well defined lesions under stereotactic immobilization and image guidance may offer great potential for achieving an improved therapeutic ratio by virtue of radiosurgical techniques. Given the high conformality along with steep dose gradients around the target volume allowing for reduced normal tissue exposure, radiosurgery may be considered as a viable modality of radiotherapeutic management. Another advantage of radiosurgery may be the completion of therapy in a usually shorter overall treatment time, which may be particularly well suited for children with

requirement of anesthesia during irradiation. Several studies have addressed the utility of radiosurgery particularly as an adjuvant or salvage treatment modality for PA. Nevertheless, despite the growing body of evidence supporting the use of radiosurgery, there is need for high level of evidence to dictate treatment decisions and establish its optimal role in management of PA. Herein, we provide a concise review of radiosurgery for PA in light of the literature.

**Key Words:** Pilocytic astrocytoma; Radiosurgery; Stereotactic irradiation; Low grade glioma; Radiation oncology; Children

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**Core Tip:** Radiosurgery for pilocytic astrocytomas may be utilized as part of initial management, as adjuvant therapy, or for salvage of recurrences. Radiosurgery offers a patient convenient procedure by a condensed treatment schedule with rapid recovery. An improved toxicity profile may be achieved through optimal normal tissue sparing. Accurate setup verification under stereotactic immobilization and image guidance may be achieved, and the procedure is convenient with regards to staff and facility workload.

## **INTRODUCTION**

Gliomas are neuroepithelial tumors arising from supporting glial cells of central nervous system (CNS). Low grade glioma (LGG) may be seen in both adults and more commonly in the pediatric population, and constitutes the most frequent CNS malignancy in children accounting for approximately one third of pediatric brain tumors<sup>[1-3]</sup>. Pilocytic astrocytoma (PA), previously referred to as polar

spongioblastoma, cystic cerebellar astrocytoma, or juvenile pilocytic astrocytoma (JPA), is a distinct histologic and biologic subset of LGG initially described by Harvey Cushing in 1931<sup>[4,5]</sup>. The term “pilocytic” has been used due to the microscopic appearance of cells with long, thin bipolar processes resembling hairs<sup>[5]</sup>. Rosenthal fibers may be typically found on hematoxylin and eosin staining as elongated eosinophilic bundles. PA comprises roughly 25% to 30% and 2% to 5% of all CNS tumors in children and in adults, respectively<sup>[6,7]</sup>. These tumors are typically classified as World Health Organization (WHO) grade I tumors<sup>[8]</sup>. Majority of PAs usually portend favorable prognosis with low growth rates, however, a more aggressive clinical course may be observed in adult PAs and pilomyxoid astrocytomas<sup>[9,10]</sup>. PAs mostly arise in the cerebellum, chiasmatic and hypothalamic areas, nevertheless, these tumors may also be seen at other locations including the cerebral hemispheres, brainstem, and the spinal cord<sup>[11]</sup>. Surgery is the main modality of management for PA, and gross total resection is intended to achieve tumor eradication<sup>[12-14]</sup>. Observation has been considered given the relatively favorable prognosis to spare patients from adverse effects of adjuvant therapy, however, failure to achieve optimal surgical tumor removal may result in subsequent recurrences and the prognosis may be affected by age, disease localization, and extent of resection<sup>[15-19]</sup>. In this context, radiation therapy (RT) may be considered in management of selected patients with PA. Irradiation has been shown to improve particularly progression free survival (PFS) for PA, nevertheless, there have been concerns over the utility of RT due to the risk of radiation induced toxicity<sup>[19-25]</sup>. Since a significant proportion of patients with PA are children with vulnerability to adverse effects of irradiation, several strategies have been introduced such as reserving RT for salvage treatment for selected patients, decreasing the total delivered doses, and improving the toxicity profile of radiation delivery through focused stereotactic irradiation<sup>[23-25]</sup>. Herein, we provide a concise review of radiosurgery for management of PA in light of the literature.

## **RADIOSURGERY FOR PILOCYTIC ASTROCYTOMA**

PA comprises a considerable proportion of LGG particularly in the pediatric population. Typically, PAs are well circumscribed WHO grade I tumors with low growth rates and indolent disease course. PAs may present in the form of solid tumors, or may include both cystic and solid components. While some patients may have no symptoms until the tumors grow into substantial size before diagnosis, symptomatic presentation may occur depending on lesion location and association with critical neurovascular structures. The disease course may also be affected by patient age with adult PAs portending typically poorer prognosis compared to JPA. Surgery is the principal therapy, however, extent of resection is a critical factor and patients undergoing incomplete surgical removal of the tumor may suffer from recurrences particularly within the first years of postoperative period<sup>[26]</sup>. While there is no consensus on radiotherapeutic management, selected patients may benefit from irradiation particularly in the setting of inoperability, incomplete resection, or recurrent disease. Conventionally fractionated RT has been traditionally utilized for radiotherapeutic management. More recently, stereotactic irradiation strategies have been introduced for improving the toxicity profile of radiation delivery without jeopardizing disease control.

Radiosurgery in the forms of stereotactic radiosurgery (SRS), hypofractionated stereotactic RT (HFSRT), and Stereotactic Body RT (SBRT) has been judiciously used for management of several CNS disorders and tumors throughout the human body with promising therapeutic outcomes<sup>[27-41]</sup>. Unique features of radiosurgical management include focused and precise targeting of well defined tumors under stereotactic immobilization and image guidance. Also, radiosurgery typically offers a condensed treatment schedule which may be particularly well suited for children with requirement of anesthesia during irradiation. While conventionally fractionated RT is delivered over 5 to 6 wk, overall treatment time is significantly reduced in radiosurgical management which includes delivery of a single or a few fractions in a significantly shorter overall

treatment time. Since a substantial proportion of patients with PA are children, requirement for daily anesthesia is a critical consideration and abbreviated treatment with radiosurgery may offer a viable radiotherapeutic approach. Multiple convergent beams are focused on the target to achieve excellent target coverage in radiosurgical applications. Steep dose gradients around the target allow for optimal normal tissue sparing, which may be of utmost importance for management of children with PA to improve the toxicity profile of radiation delivery. The need for expanding the target with margins to account for setup uncertainties is eliminated or minimized under image guidance and robust stereotactic immobilization of the patients which may contribute to reduced normal tissue exposure in radiosurgery of PAs. Table 1 shows summarized data from selected series of stereotactic irradiation for management of PA in pediatric and adult patients.

Murphy *et al* assessed outcomes of GKSRS for PA<sup>[42]</sup>. Median patient age was 14 years (range: 2-84 years) at the time of GKSRS. Median tumor volume was 3.45 cc (range: 0.17-33.7 cc). Median margin dose was 14 Gy (range: 4-22.5 Gy). At last follow-up, 5-year and 10-year overall survival (OS) rates were 95.7% and 92.5% respectively while 5-year and 10-year PFS rates were 74.0% and 69.7%, respectively. In this largest study of single session GKSRS including 141 patients from 9 International Radiosurgery Research Foundation centers, the authors concluded that GKSRS provided favorable long term PFS and OS<sup>[42]</sup>.

Trifiletti *et al* from the University of Virginia evaluated GK-based stereotactic irradiation in a series of 28 patients with PA<sup>[43]</sup>. Median age was 17.4 years (range: 2-70.3 years). Median tumor volume was 1.84 cc and the median margin dose was 16 Gy. One patient received multi-fraction SRS with a total dose of 15 Gy delivered in 3 fractions. Local tumor control rate was 93% without adverse radiation effects. Actuarial PFS rates at 1, 3, 6, and 12 years were 96%, 96%, 96%, and 80%, respectively. Authors concluded that favorable tumor control rates may be achieved by SRS as a viable technique for management of PA in the primary or recurrent disease setting<sup>[43]</sup>.

Simonova *et al* assessed long term outcomes with GK-based stereotactic irradiation for PA<sup>[44]</sup>. Their series included 25 pediatric patients with a median age of 13 years (range: 3-17 years). Median target volume was 2.7 cc (range: 0.2-25 cc). The 10-year OS and PFS rates were 96% and 80%, respectively. Patients with a planning target volume of 2.7 cc or less had increased PFS. Authors concluded that radiosurgery offers an alternative treatment modality providing long term local control for management of small residual or recurrent PAs <sup>[44]</sup>.

Lizarraga *et al* evaluated linear accelerator (LINAC)-based stereotactic irradiation for progressive residual pilocytic astrocytomas in a series of 12 patients<sup>[45]</sup>. Median age at the start of stereotactic irradiation was 21 years (range: 5-41 years). There were no radiation induced adverse effects in the follow-up period, and probabilities of long term PFS and disease specific survival were 73.3% and 91.7%, respectively<sup>[45]</sup>.

Hallemeier *et al* assessed GKSRS for management of recurrent or unresectable PA in a series of 18 patients treated at the Mayo Clinic<sup>[46]</sup>. Median age at GKSRS was 23 years (range: 4-56 years). Median treatment volume for GKSRS was 9.1 cc. Median margin dose was 15 Gy and 16 Gy for patients with and without prior RT, respectively. PFS rates were 65%, 41%, and 17% at 1, 5, and 10 years, respectively at a median follow-up duration of 8 years. OS rates were 94%, 71%, and 71%, at 1, 5, and 10 years after GKSRS, respectively. The authors concluded that GKSRS may serve as a meaningful therapeutic option for management of recurrent or unresectable PAs in the setting of treatment failure with surgery and/or external beam RT considering the durable local tumor control and low permanent radiation induced morbidity with GKSRS<sup>[46]</sup>.

Kano *et al* evaluated GKSRS for management of newly diagnosed or recurrent JPAs in a series of 50 pediatric patients with a median age of 10.5 years (range: 4.2-17.9 years)<sup>[47]</sup>. Median margin dose was 14.5 Gy. PFS after GKSRS (including tumor growth and cyst enlargement) was 91.7%, 82.8% and 70.8% at 1, 3 and 5 years, respectively for the entire series at a median follow-up duration of 55 mo. The authors concluded that response to treatment was better in small volume residual solid JPAs and GKSRS

should be considered when resection is not feasible or in the presence of early recurrence<sup>[47]</sup>.

In another study, Kano *et al* separately assessed GKSRS for management of PA in adult patients<sup>[48]</sup>. A total of 14 patients treated using GKSRS between 1994 and 2006 were included. Median age was 32 years (range: 19-52 years). Median margin dose was 13.3 Gy, and median radiosurgery target volume was 4.7 cc. At a median follow-up duration of 36.3 mo, 3 patients died and 11 patients were alive with OS rates of 100%, 88.9% and 88.9% at 1, 3 and 5 years, respectively for the entire series. The authors emphasized that PA could behave more aggressively in adult patients, and thus additional treatment strategies could be considered for unresectable PAs located at critical brain areas. The authors concluded that GKSRS was <sup>4</sup>most valuable for patients after maximal feasible surgical resection and delayed cyst progression contributed to late loss of tumor control<sup>[48]</sup>.

Hadjipanayis *et al* performed a retrospective analysis of 37 patients receiving GKSRS at the University of Pittsburgh Medical Center for recurrent or critically located PAs<sup>[49]</sup>. Median age at GKSRS was 14 years. At a median follow-up duration of 28 mo after GKSRS and 59 mo after diagnosis, 33 (89%) out of 37 patients were alive, providing a 7-year actuarial survival rate of 76%. Follow-up imaging revealed tumor control in 25 (68%) out of 37 patients. While 10 patients had complete resolution of tumor, 8 patients had greater than 50% reduction in tumor volume. There were no procedure related permanent morbidity or mortality. The authors concluded that GKSRS could be used as part of multimodal management for progressive, recurrent, or unresectable PAs and GKSRS could replace fractionated RT and chemotherapy in selected patients as a safe and promising treatment modality<sup>[49]</sup>.

Boëthius *et al* evaluated outcomes of 19 patients receiving GKSRS for PA<sup>[50]</sup>. Mean age was 10.6 years, and the study group included 16 pediatric patients. Median tumor volume was 2.2 cc. A median marginal dose of 10 Gy was used given that majority of tumors were localized within or in close neighborhood of the brainstem. A satisfactory tumor control rate of 94.7% was achieved at a median radiological follow-



up duration of 4.7 years and median clinical follow-up duration of 7 years albeit with a relatively lower GKSRS dose<sup>[50]</sup>.

Somaza *et al* from Pittsburgh University assessed the utility of GKSRS in adjuvant treatment of 9 pediatric patients with growing and unresectable deeply seated PAs<sup>[51]</sup>. Mean margin dose was 15 Gy. At a mean follow-up duration of 19 mo, tumor control was achieved in all patients with significant tumor shrinkage in 5 patients and no further growth in 4 patients. No patients had early or late toxicity. The authors concluded that GKSRS served as a safe and effective therapeutic modality for management of deeply seated and small volume PAs<sup>[51]</sup>.

Overall, stereotactic irradiation has been utilized for management of PA in both children and adults as a promising treatment modality. Since adverse effects of irradiation constitute major concerns over the use of RT for treatment of PAs, improving the toxicity profile of radiation delivery is a critical aspect of contemporary patient management in the millennium era. Within this context, focused and precise targeting of well circumscribed PAs under stereotactic immobilization and image guidance may offer great potential for achieving an improved therapeutic ratio by virtue of radiosurgical techniques. Another advantage of radiosurgery may be the completion of therapy in a usually shorter overall treatment time, which may be particularly well suited for children with requirement of anesthesia during irradiation. Although radiosurgery is a relatively newer treatment paradigm compared to conventional RT, it has gained widespread popularity and adoption with growing body of evidence supporting its utility. Nevertheless, there is still room for further improvements with the need for high level of evidence to reach multidisciplinary consensus for optimal management of PAs.

## **CONCLUSION**

PA may be seen in both adults and children as a distinct histologic and biologic subset of LGG. Surgery is the principal treatment for management of PAs, however, selected patients may benefit from irradiation particularly in the setting of inoperability,

incomplete resection, or recurrent disease. While conventionally fractionated RT has been traditionally utilized for radiotherapeutic management, stereotactic irradiation strategies have been introduced more recently to improve the toxicity profile of radiation delivery without compromising tumor control. PAs may be suitable for radiosurgical management due to their typical appearance as well circumscribed lesions. Focused and precise targeting of these well defined lesions under stereotactic immobilization and image guidance may offer great potential for achieving an improved therapeutic ratio by virtue of radiosurgical techniques. <sup>3</sup> Given the high conformality along with steep dose gradients around the target volume allowing for reduced normal tissue exposure, radiosurgery may be considered as a viable modality of radiotherapeutic management. Another advantage of radiosurgery may be the completion of therapy in a usually shorter overall treatment time, which may be particularly well suited for children with requirement of anesthesia during irradiation.

Although radiosurgery has a shorter history compared to conventional RT, there is accumulating data on its utility for management of several tumors throughout the human body. In the context of PAs, several studies have addressed its use particularly as an adjuvant or salvage treatment modality. Nevertheless, despite the growing body of evidence supporting the utility of radiosurgery, there is need for high level of evidence to dictate treatment decisions and establish its optimal role in management of PA. We believe that both SRS and SRT may be considered as viable radiosurgical methods for management of PA and selection between SRS and SRT should be based on patient, tumor, and treatment characteristics.

In the context of future perspectives, immunotherapy, identification of driver alterations and introduction of efficacious targeted therapies may pave the way for contemporary treatment approaches for PAs. Further extensive investigation is warranted to develop safe and effective treatment strategies for management of PAs.

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