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**Concise review of stereotactic irradiation for pediatric glial neoplasms: Current concepts and future directions**

Sager O *et al*. Stereotactic irradiation for pediatric glial neoplasms

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**Abstract**

Brain tumors, which are among the most common solid tumors in childhood, remain a leading cause of cancer-related mortality in pediatric population. Gliomas, which may be broadly categorized as low grade glioma and high grade glioma, account for the majority of brain tumors in children. Expectant management, surgery, radiation therapy (RT), chemotherapy, targeted therapy or combinations of these modalities may be used for management of pediatric gliomas. Several patient, tumor and treatment-related characteristics including age, lesion size, grade, location, phenotypic and genotypic features, symptomatology, predicted outcomes and toxicity profile of available therapeutic options should be considered in decision making for optimal treatment. Management of pediatric gliomas poses a formidable challenge to the physicians due to concerns about treatment induced toxicity. Adverse effects of therapy may include neurological deficits, hemiparesis, dysphagia, ataxia, spasticity, endocrine sequelae, neurocognitive and communication impairment, deterioration in quality of life, adverse socioeconomic consequences, and secondary cancers. Nevertheless, improved understanding of molecular pathology and technological advancements may pave the way for progress in management of pediatric glial neoplasms. Multidisciplinary management with close collaboration of disciplines including pediatric oncology, surgery, and radiation oncology is warranted to achieve optimal therapeutic outcomes. In the context of RT, stereotactic irradiation is a viable treatment modality for several central nervous system disorders and brain tumors. Considering the importance of minimizing adverse effects of irradiation, radiosurgery has attracted great attention for clinical applications in both adults and children. Radiosurgical applications offer great potential for improving the toxicity profile of radiation delivery by focused and precise targeting of well-defined tumors under stereotactic immobilization and image guidance. Herein, we provide a concise review of stereotactic irradiation for pediatric glial neoplasms in light of the literature.

**Key Words:** Radiosurgery; Stereotactic irradiation; Stereotactic radiosurgery; Pediatric glioma; Gamma knife; Linear accelerator

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**Core Tip:** Pediatric gliomas comprise the majority of brain tumors in children. Radiotherapeutic management of pediatric gliomas poses a formidable challenge considering the adverse effects of irradiation for this vulnerable patient population. In this context, efforts have been focused on improving the toxicity profile of radiation delivery. Stereotactic irradiation with stereotactic radiosurgery or stereotactic radiotherapy in a single or few treatment fractions may serve as a viable radiotherapeutic approach to achieve this goal given the high conformality along with steep dose gradients around the target volume allowing for reduced normal tissue exposure under precise immobilization and image guidance.

**INTRODUCTION**

Brain tumors, which are among the most common solid tumors in childhood, remain a leading cause of cancer-related mortality in pediatric population[1-3]. Gliomas, which may be broadly categorized as low grade glioma (LGG) and high grade glioma (HGG), account for the majority of brain tumors in children[4]. Expectant management, surgery, radiation therapy (RT), chemotherapy, targeted therapy or combinations of these modalities can be used to manage pediatric gliomas. Several patient, tumor and treatment-related characteristics including age, lesion size, grade, location, phenotypic and genotypic features, symptomatology, predicted outcomes and toxicity profile of available therapeutic options should be considered in decision making for optimal treatment[4-6]. Management of pediatric gliomas poses a formidable challenge to the physicians owing to concerns about treatment induced toxicity. Adverse effects of therapy for this vulnerable patient population may include neurological deficits, hemiparesis, dysphagia, ataxia, spasticity, endocrine sequelae, growth abnormalities, audiovisual toxicity, neurocognitive and communication impairment, deterioration in quality of life, adverse socioeconomic consequences, and secondary cancers[7-10]. Nevertheless, improved understanding of molecular pathology and technological advancements may improve management of pediatric glial neoplasms. Multidisciplinary management with close collaboration of disciplines including pediatric oncology, surgery, and radiation oncology is warranted to achieve optimal therapeutic outcomes[11-14].

In the context of RT, stereotactic irradiation represents a viable treatment modality for several central nervous system disorders (CNS) and brain tumors[15-19]. Considering the importance of minimizing adverse effects of irradiation, radiosurgery has attracted critical attention for clinical applications in both adults and children. Radiosurgical applications offer great potential for improving the toxicity profile of radiation delivery by focused and precise targeting of well-defined tumors under stereotactic immobilization and image guidance. Herein, we provide a concise review of stereotactic irradiation for pediatric glial neoplasms in light of the literature.

**STEREOTACTIC IRRADIATION FOR PEDIATRIC HGG**

Based on the classification of World Health Organization (WHO) in 2016, HGG comprises glioblastoma, anaplastic astrocytoma, and diffuse midline glioma including diffuse intrinsic pontine glioma (DIPG)[20]. Pediatric HGG accounts for approximately 8%-12% of all childhood CNS tumors and it is the leading cause of cancer-related mortality in children under 19 years of age[21-24]. Pediatric HGG usually follows an aggressive disease course which results in morbidity and mortality, however, there are several distinctive features of pediatric HGG regarding natural history, causative genetic mutations, response to treatment, and tumor localization within the brain[6,22,25-28]. While HGG frequently arises from LGG with malignant transformation in adults, this is very uncommon in pediatric patients with differences in genetic and epigenetic features. Similar to adult HGG, surgery is the primary treatment modality for management of pediatric HGG, and the extent of resection is a significant prognostic factor[29-34]. Surgery alone may be insufficient for optimal management, and adjunctive therapies including RT and chemotherapy are recommended. Gross total resection of HGG is usually difficult owing to the infiltrative nature of the disease and the risk of excessive toxicity particularly when the lesions are located in close vicinity of critical neurovascular structures[22,35,36]. Microscopic tumor cells may still remain even after gross total resection with potential for subsequent recurrence. Due to the increased vulnerability of younger children to adverse effects of ionizing radiation and the relatively favorable disease course, RT is typically deferred for this subgroup of patients under 3 years of age by considering other therapeutic options[37-39]. Nevertheless, older children are frequently referred for postoperative RT with concurrent and adjuvant chemotherapy[6,22,29,40]. In the context of RT for pediatric HGG, conventional fractionation is common practice owing to lack of superiority of altered fractionation regimens[41-44]. Of note, several series investigated the utility of hypofractionated RT regimens especially for DIPG[44-47]. Compared to conventionally fractionated RT delivered over 5 wk to 6 wk, hypofractionated RT schedules may offer reduction in number of anesthesia administrations for patients treated under anesthesia and less burden on patients, parents, and treatment centers.

Radiation dose escalation strategies, combined modality treatment approaches, and incorporation of contemporary RT techniques such as radiosurgery are being investigated to improve the therapeutic ratio for HGG in view of the aggressive disease course and poor treatment outcomes despite intensive management. Stereotactic irradiation is a common RT technique for treatment of adult HGG and several studies support its use for this indication either as part of initial management or as salvage therapy[18,19,48-51]. Data on stereotactic irradiation of HGG have been mostly extracted from the literature including adult patients considering that there is paucity of data about pediatric HGG. Survival after hypofractionation (including radiosurgical treatments) in glioblastoma has been assessed in a recent meta-analysis and systematic review[52]. Meta-analysis of eleven comparative studies regarding first line management of glioblastoma with hypofractionated *vs* conventionally fractionated irradiation revealed no significant difference between the two fractionation schemes, and hypofractionation has been suggested as a reasonable alternative fractionation scheme for selected patients[52]. In the context of radiosurgery, a phase III randomized trial conducted by the Radiation Therapy Oncology Group reported no survival advantage with the addition of stereotactic irradiation to conventional external beam RT[53]. Nevertheless, there is active investigation on the utility of stereotactic irradiation for achieving improvements in treatment outcomes of patients with HGG. Stereotactic irradiation is an extreme form of focal RT which is used to deliver high doses of radiation in a single or a few fractions to well-defined lesions. Minimal exposure of normal tissues due to steep dose gradients around the target volume may be achieved with radiosurgery. While several studies have reported improved treatment outcomes with incorporation of stereotactic irradiation for adult HGG, there is paucity of data on the utility of radiosurgery for pediatric HGG[54-61].

Giller *et al*[58] reported outcomes of robotically guided radiosurgery for pediatric brain tumors. Twenty-one patients aged between 8 mo and 16 years received Cyberknife radiosurgery for pilocytic astrocytomas, anaplastic astrocytomas, ependymomas, atypical teratoid/rhabdoid tumors, medulloblastomas, craniopharyngiomas, and other pathologies which were deemed unresectable[58]. Local control was achieved in patients with anaplastic astrocytoma, and the authors concluded that Cyberknife radiosurgery could be used for achieving local control of selected pediatric brain tumors with elimination of the requirement for rigid head fixation[58]. In another series of 90 children receiving stereotactic radiosurgery (SRS) for brain tumors at the Joint Center for Radiation Therapy during a 10-year period between 1987 and 1997, 20% of the patients (18 patients) had pediatric HGG[59]. Out of the total 90 patients, 10 patients (11%) had glioblastoma and 8 patients (9%) had anaplastic astrocytoma[59]. Median progression free survival (PFS) was 12 mo (range: 3-119 mo) and median 3-year actuarial local control rate was 50% for the 18 patients with glioblastoma and anaplastic astrocytoma[59]. Four patients receiving SRS as part of initial management were alive and free of progression at 50, 62, 66, and 119 mo, respectively[59]. Baumann *et al*[60] reported their experience with pediatric radiosurgery in a series of 52 patients. Local control was worse in patients with HGG compared to LGG[60]. Grabb *et al*[61] assessed the role of SRS in 25 pediatric patients with surgically incurable glial tumors treated between 1988 and 1994. Twelve patients had malignant astrocytomas or ependymomas. While 7 children died of disease with a median survival of 6 mo after SRS, 5 children were alive at 12, 45, 50, 72, and 72 mo after radiosurgical management[61].

In summary, stereotactic irradiation may be considered as a viable therapeutic strategy for management of adult HGG particularly in the recurrent disease setting. There is scarce literature regarding the utility of stereotactic irradiation for HGG in children, however, this advanced radiotherapeutic technology may offer benefits for pediatric patients and deserves further investigation to improve normal tissue sparing through precise stereotactic localization under image guidance.

**STEREOTACTIC IRRADIATION FOR PEDIATRIC LGG**

Pediatric LGG is the most common CNS neoplasm among children[5,30]. Most common subtype of pediatric LGG is pilocytic astrocytoma, and other subtypes are diffuse astrocytoma (fibrillary, gemistocytic, or protoplasmic), subependymal giant cell astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, gangliocytoma, desmoplastic infantile ganglioglioma, and dysembryoplastic neuroepithelial tumor[5,23]. Prognosis for these heterogeneous group of tumors is usually favorable, thus toxicity profile of management is very important[62-65]. Location and extent of disease are critical factors which should be considered in decision making for treatment of pediatric LGG. Other important factors include age, symptomatology, phenotypic and genotypic features, predicted outcomes and toxicity profile of available therapeutic options. Optimal care of patients with pediatric LGG may require incorporation of multimodality management with close collaboration of pediatric oncology, surgery, and radiation oncology disciplines[64,65]. Surgical resection is the principal mode of management for tumors which are amenable to surgery. Observation may be considered after surgical removal of the tumor to spare pediatric patients from potential toxicity of adjunctive therapies. Previous data on pediatric and adult patients have shown improvements in treatment outcomes with incorporation of RT in management of LGG[66,67]. There have been significant advances in the disciplines of pediatric neurosurgery and radiation oncology over the years[12-14]. Despite advances in therapy, irradiation for pediatric brain tumors still remains to be a challenge given the vulnerability of children to adverse RT effects such as neuroendocrine and neurocognitive deficits, growth abnormalities, audiovisual toxicity, deterioration in quality of life, adverse socioeconomic consequences, and secondary cancers[7-10,68]. Nevertheless, optimal surgical management may not be feasible for tumors at critical locations such as the optic pathway, brainstem, basal ganglia, thalamus, hypothalamus, and other eloquent brain areas. Therefore, irradiation in the form of radiosurgery or conventionally fractionated RT may be considered in the presence of surgically inaccessible tumors, incomplete excision, or recurrence. Conformal RT techniques, particle therapy, and radiosurgical treatments may offer reduced normal tissue exposure in management of pediatric LGG[68-72]. Among the radiotherapeutic options for treatment of pediatric LGG, stereotactic irradiation offers a viable RT technique. Radiosurgery is a very highly focused form of therapeutic irradiation with the potential of improving the toxicity profile of radiation delivery through steep dose gradients around the target volume. Pilocytic astrocytomas, the most common of pediatric LGG, are typically visualized as well-defined lesions on neuroimaging which renders them more suitable for radiosurgical management. While infiltrative nature of the disease comprises a challenging aspect in radiosurgery for HGG, most LGG lesions with well-defined borders are suitable for treatment with stereotactic irradiation. Several studies including pediatric patients have addressed the utility of stereotactic irradiation in LGG management either as primary, adjuvant, boost or salvage therapy[73-88]. Table 1 shows summarized data from selected series of stereotactic irradiation for LGG including pediatric patients.

Barcia *et al*[73] reported their experience with SRS for deeply seated inoperable LGG in a series of 16 patients including 8 children. Histological confirmation of LGG was available for 7 patients, and 12 patients had received prior irradiation. Median age was 20 years (range: 4-68 years). Cobalt source and stereo guide were used for either primary or boost therapy with a mean margin dose of 21.7 Gy. Complete response was achieved for 8 patients (50%), and tumor shrinkage or stabilization was detected in 5 patients (31%) corresponding to a tumor control rate of 81%. Three patients (19%) who had brainstem glioma succumbed to their disease with no response to SRS. The authors concluded that radiosurgery could serve as an effective therapeutic modality for management of deeply seated LGG[73].

Somaza *et al*[74] from Pittsburgh University investigated the role of gamma knife SRS (GKSRS) in adjuvant treatment of 9 children with deeply seated, growing and unresectable pilocytic astrocytomas. Lesions had a mean diameter of 16 mm and were localized at cerebellar peduncle, dorsolateral pons, midbrain, thalamus, hypothalamus, caudate nucleus, and temporal lobe. 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 suffered from early or late toxicity. The authors concluded that GKSRS proved to be safe and effective for management of deeply seated and small volume pilocytic astrocytomas[74].

Kida *et al*[75] reported long term outcomes of GKSRS in the management of low grade astrocytomas in a large series of 51 patients from Japan. The study included 12 pediatric patients with a mean age of 9.8 years. Tumor control rate was 91.7% for WHO grade I astrocytomas and 87.2% for WHO grade II astrocytomas. Mean margin dose was 12.5 Gy for WHO grade I astrocytomas and 15.7 Gy for WHO grade II astrocytomas. Higher treatment response was achieved in patients ≥ 10 years of age with WHO grade I astrocytomas and for those with follow-up duration exceeding 2 years. The authors concluded that radiosurgery could play an important role in management of low grade astrocytomas and complete cure could be expected at least for some patients[75].

Boëthius *et al*[76] from Sweden reported outcomes of 19 patients receiving GKSRS for pilocytic astrocytoma at Karolinska Hospital. Mean age was 10.6 years (range: 2-60 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 since majority of tumors were located within or in close vicinity of the brainstem. At a median radiological follow-up duration of 4.7 years and median clinical follow-up duration of 7 years, a satisfactory tumor control rate of 94.7% was achieved despite the relatively lower GKSRS dose[76].

Hadjipanayis *et al*[77] assessed outcomes of 49 patients (including 29 children) receiving GKSRS at the Pittsburgh University for LGG. Involved locations included the brainstem in 22 patients, thalamus in 6 patients, temporal lobe in 5 patients, cerebellum in 4 patients, frontal lobe in 4 patients, parietal lobe in 3 patients, insular cortex in 1 patient, hypothalamus in 1 patient, third ventricle in 1 patient, corpus callosum in 1 patient, and optic tract in 1 patient. Median age was 14 years (range: 3-52 years) for the 37 patients with pilocytic astrocytoma including 25 children aged ≤ 18 years. Median age was 25 years (range: 5-57 years) for the 12 patients with WHO Grade II fibrillary astrocytoma including 4 children aged ≤ 18 years. Median margin dose was 15 Gy and 16 Gy for pilocytic astrocytomas and WHO Grade II fibrillary astrocytomas, respectively. Overall, serial neuroimaging after GKSRS revealed complete tumor resolution in 11 patients, reduced tumor volume in 12 patients, stable tumor volume in 10 patients, and delayed tumor progression in 16 patients. Out of the 37 patients with pilocytic astrocytoma, tumor control was achieved in 25 patients (68%). Out of the 12 patients with WHO Grade II fibrillary astrocytoma, tumor control was achieved in 8 patients (67%). The authors concluded that SRS offers a safe and promising therapeutic modality for management of selected patients with pilocytic astrocytomas or WHO Grade II fibrillary astrocytomas[77].

Saran *et al*[78] from Royal Marsden Hospital reported outcomes of stereotactically guided conformal radiotherapy (SCRT) in the management of progressive or inoperable pediatric LGG. Median age was 6 years (range: 5-16 years). Fourteen patients received linear accelerator (LINAC)-based SCRT in 30-33 daily fractions, and the total dose was 50-55 Gy. Lesion locations included the optic chiasm in 9 patients, third ventricle in 2 patients, pineal region in 1 patient, craniocervical junction in 1 patient, and hypothalamus in 1 patient. Median tumor volume was 19.5 cc (range: 7.5-180 cc). Median follow-up duration was 33 mo. The 3-year local PFS and overall survival rate following SCRT was 87% and 100%, respectively. The authors concluded that SCRT offers a feasible and high precision technique for stereotactic irradiation of pediatric LGG[78].

Marcus *et al*[79] from Dana-Farber Cancer Institute assessed the efficacy of LINAC-based stereotactic radiotherapy (SRT) for management of small, localized, pediatric brain tumors. Their prospective study included 50 patients with LGG. Out of the 50 patients, 35 patients had WHO grade I astrocytoma and 15 patients had WHO grade II astrocytoma. Median age was 9 years (range: 2-26 years). Out of the 50 patients, 38 patients had progression after surgery and 12 patients had progression after chemotherapy. Mean total dose for SRT was 52.2 Gy delivered in 1.8-Gy daily fractions. With a median follow-up duration of 6.9 years, PFS rate was 82.5% at 5 years and 65% at 8 years. Overall survival was 97.8% and 82% at 5 and 8 years, respectively. There were 6 cases of local progression all within the primary tumor bed. There was no marginal failure. The authors concluded that SRT offers excellent local control for small, localized LGG in children and limited margins with stereotactic immobilization and planning techniques could be considered to minimize late sequelae in view of no marginal failures in the study[79].

Wang *et al*[80] reported outcomes of GKSRS for 21 patients with 25 histologically proven low grade astrocytomas treated at the Taipei Veterans General Hospital. Median age was 20 years (range: 6-70 years). Median margin dose was 14.5 Gy. With a median radiological follow-up duration of 49 mo and median clinical follow-up duration of 67 mo, all patients with pilocytic astrocytoma were free from tumor progression. Complete tumor remission was achieved in 3 patients. PFS rate was 65% at 10 years. The authors suggested reduction in GKSRS dose to prevent excessive toxicity in the setting of combined use of GKSRS and RT. The authors concluded that GKSRS may be utilized for management of selected patients with low grade astrocytomas to achieve durable long term local tumor control rates with acceptable toxicity[80].

Kano *et al*[81] from Pittsburgh University assessed GKSRS outcomes for management of newly diagnosed or recurrent juvenile pilocytic astrocytomas. Their series included 50 pediatric patients with a median age of 10.5 years (range: 4.2-17.9 years). Lesion locations included the cerebellum in 20 patients, brainstem in 13 patients, cerebral hemispheres in 7 patients, basal ganglia in 6 patients, and ventricles in 4 patients. Out of the total 50 patients, only 5 patients had received prior fractionated RT ± chemotherapy. Median margin dose was 14.5 Gy. Median follow-up duration was 55 mo. For the entire series, PFS after GKSRS (including tumor growth and cyst enlargement) was 91.7%, 82.8% and 70.8% at 1, 3 and 5 years, respectively. Univariate analysis revealed that solid lesion, target volume < 8 cc, newly diagnosed disease, and no brainstem involvement were prognostic factors for improved PFS with statistical significance. The authors concluded that treatment response was better in small volume residual solid juvenile pilocytic astrocytomas and GKSRS should be considered if resection is not feasible or in the presence of early recurrence[81].

Henderson *et al*[82] reported the Indiana University experience with GKSRS for low grade astrocytoma management in a series of 12 patients. Median age was 17.4 years (range: 5.9-63 years). A total of 13 lesions were treated using a median margin dose of 13 Gy. With a median follow-up duration of 48.2 mo, 2- and 4-year tumor control rates were 84.6% and 76.9, respectively. Overall survival and PFS rates were 83.3% and 75% at 4 years, respectively. The authors concluded that GKSRS could provide local control for carefully selected patients with unresectable or recurrent low grade astrocytomas[82].

Weintraub *et al*[83] from Virginia University reported outcomes of GKSRS for management of 24 pediatric patients. Median age was 11 years (range: 4-18 years). Out of the 24 patients, 15 patients were diagnosed with WHO grade I astrocytoma and 4 patients were diagnosed with WHO grade II LGG by histopathological assessment. Mean tumor volume was 2.4 cc and median margin dose was 15 Gy. Median radiological follow-up duration was 74 mo and median clinical follow-up duration was 144 mo. Complete resolution of tumor was achieved in 5 patients (21%) and ≥ 50% reduction in tumor size was achieved in 18 patients (75%). The authors concluded that GKSRS offers good clinical control of residual or recurrent gliomas in pediatric patients[83].

Hallemeier *et al*[84] reported outcomes of 18 patients (including 6 children) treated with GKSRS for recurrent or unresectable pilocytic astrocytoma at the Mayo Clinic. Median age was 23 years (range: 4-56 years). One or more prior surgical resection was performed in 13 patients (72%). Ten patients (56%) had received previous conventionally fractionated external beam RT and 4 patients (22%) had received prior systemic chemotherapy. Median treatment volume for GKSRS was 9.1 cc. Median margin dose was 15 Gy for previously irradiated patients and 16 Gy for patients without prior RT. Median follow-up duration was 8 years. PFS rates were 65%, 41%, and 17% at 1, 5, and 10 years, respectively. Overall survival rates were 94%, 71%, and 71%, at 1, 5, and 10 years after GKSRS, respectively. Prior external beam RT was found to be associated with inferior overall survival and PFS outcomes. The authors concluded that GKSRS could serve as a meaningful therapeutic option for management of recurrent or unresectable pilocytic astrocytomas when surgery and/or external beam RT fails[84].

Lizarraga *et al*[85] from the University of California reported outcomes of LINAC-based stereotactic irradiation for progressive/residual pilocytic astrocytomas in a series of 12 patients (including 5 children < 18 years of age). Median age at the start of stereotactic irradiation was 21 years (range: 5-41 years). All patients had undergone upfront partial surgical debulking as initial management without adjuvant chemotherapy or RT. Salvage stereotactic irradiation was considered in the setting of local progression. LINAC-based SRS was used to treat a median target volume of 1.69 cc in 3 patients with a median dose of 18.75 Gy. LINAC-based SRT with a median total dose of 50.4 Gy was used to treat a median target volume of 6.5 cc in 9 patients. No radiation induced adverse effects were observed in the study, and probabilities of long term PFS and disease specific survival were 73.3% and 91.7%, respectively[85].

Simonova *et al*[86] from Prag assessed long term outcomes of GK-based SRS or SRT for pilocytic astrocytomas in a series of 25 pediatric patients. Median age was 13 years (range: 3-17 years)[86]. Selection of single fraction or fractionated stereotactic irradiation was based on lesion size, location and proximity to surrounding critical structures. Median target volume was 2.7 cc (range: 0.2-25 cc). Five patients (20%) received single fraction radiosurgery with a median dose of 16 Gy. Twenty patients (80%) received stereotactic irradiation in 5 or 10 fractions using a median dose of 25 Gy. The 10-year overall survival and PFS rates were 96% and 80%, respectively. A significantly better PFS was observed in patients with a planning target volume of 2.7 cc or less. The authors concluded that radiosurgery offers an alternative therapeutic modality for management of small residual or recurrent pilocytic astrocytomas providing long term local control[86].

Trifiletti *et al*[87] reported outcomes of 28 patients receiving GK-based stereotactic irradiation for management of pilocytic astrocytomas at the University of Virginia. Median age was 17.4 years (range: 2-70.3 years). Single fraction GKSRS was performed in 27 patients, and 1 patient received stereotactic irradiation in 3 fractions. Median tumor volume was 1.84 cc and median margin dose was 16 Gy. Median clinical follow-up duration was 5.2 years and median radiological follow-up duration was 4.6 years. Local tumor control rate was 93% without adverse radiation effects. Actuarial PFS rates were 96%, 96%, 96%, and 80% at 1, 3, 6, and 12 years, respectively. The authors concluded that SRS offers an appropriate technique for management of pilocytic astrocytomas in the primary or recurrent disease setting with favorable tumor control rates and infrequent clinical toxicity[87].

Gagliardi *et al*[88] assessed long term outcomes of GKSRS for LGG. Their series of 39 patients included 10 pediatric patients. Median age was 31 years (range: 9-72 years). Most common histology was pilocytic astrocytoma. Median tumor volume was 1.24 cc. Median margin dose was 15 Gy. Median follow-up duration was 54.5 mo. Actuarial PFS rates at 1, 5, and 10 years were 74.9%, 52.8%, and 39.1%, respectively. Assessment of patients’ quality of life and functional performance was performed by utilization of standardized functional performance scores and validated subjective health survey questionnaires. Clinical improvement and Karnofsky Performance Status improvement were observed in 52.4% and 45.5% of the patients, respectively. The authors concluded that GKSRS may serve as a viable therapeutic modality for management of LGG which may provide tumor growth control and improve patients’ functional performance and quality of life with optimization of social functioning and minimization of disease-related psychological impact[88].

In summary, stereotactic irradiation has been more frequently incorporated into management of pediatric LGG as compared to adult HGG. Pilocytic astrocytoma accounts for the majority of pediatric LGG and may be considered as suitable for radiosurgical treatment with its well-defined borders on neuroimaging. Clearly, several other factors are critical in decision making for stereotactic irradiation of a pediatric patient with LGG. Stereotactic irradiation has been used as primary therapy in the presence of deeply seated lesions at eloquent brain areas, or as a boost treatment in conjunction with conventionally fractionated external beam RT, and more frequently to treat progressive or recurrent pediatric LGG (Table 1)[73-88]. Overall, these series reported favorable tumor control rates with stereotactic irradiation. Improvements have been observed in clinical symptoms, functional performance and quality of life parameters with low rates of severe toxicity. However, there is still room for improvement with the need for accumulation of further robust and high level evidence to consider stereotactic irradiation as a standard part of management for pediatric LGG.

**CONCLUSION**

Pediatric brain tumors are the most common solid tumors in children which may lead to morbidity and mortality. Gliomas comprise the majority of brain tumors in children. Radiotherapeutic management of gliomas in children poses a formidable challenge considering the adverse effects of irradiation for this vulnerable patient population. In this context, efforts have been focused on improving the toxicity profile of radiation delivery. Stereotactic irradiation with SRS or SRT in a single or few treatment fractions may serve as a viable radiotherapeutic approach to achieve this goal. High conformality along with steep dose gradients around the target volume allows for reduced normal tissue exposure under precise immobilization and image guidance. While conventionally fractionated RT regimens administered over 5 wk to 6 wk may lead to substantial burden on children particularly when daily anesthesia is needed, radiosurgical approaches allow for abbreviated treatment courses. Also, margin-free strategies may be considered in the setting of stereotactic irradiation with precise immobilization and image guidance for management of well demarcated lesions such as pilocytic astrocytomas[89].

Overall, stereotactic irradiation has been utilized less frequently for HGG and more commonly for LGG in children[58-61,73-89]. Some of the studies reporting data on stereotactic irradiation of pediatric gliomas also included adult patients. Drawing firm conclusions may be confounded by diversities in patient, tumor, and treatment characteristics in studies with limited number of patients and inherent limitations. Nevertheless, available limited data on stereotactic irradiation of pediatric gliomas suggest potential utility of this contemporary approach as part of initial management or for treatment of progressive or recurrent lesions despite the need for further supporting evidence.

In the context of future directions, immunotherapy, identification of driver alterations and introduction of effective targeted therapies may pave the way for innovatory treatment strategies for children with pediatric glial neoplasms[90-93]. There is need for active investigation on development of safe and efficacious therapeutic approaches for management of pediatric glial neoplasms.

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**Footnotes**

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**Table 1 Selected series of stereotactic irradiation for low grade glioma including pediatric patients**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study period** | **Number of patients** | **Proportion of pediatric patients (%)** | **Histology** | **Setting** | **Treatment** | **Dose (Gy)** | **Age (yr)** | **Tumor size** | **Prior irradiation** | **Follow-up duration** | **Tumor control or PFS (%)** |
| Barcia *et al*[73], 1994 | 1978-1991 | 16 | 50 | LGG | Primary or boost therapy | SRS by use of a cobalt source and stereoguide | Mean margin dose 21.7 Gy | Median age 20 yr (range: 4-68 yr) | - | 12 patients | Median 50 mo | Tumor control 81 |
| Somaza *et al*[74], 1996 | 1990-1993 | 9 | 100 | Pilocytic astrocytoma | Adjuvant or salvage therapy | GKSRS | Median margin dose 15 Gy | Mean age 8.6 yr (range: 4-17 yr) | Mean tumor diameter 16 mm  | 2 patients | Median 19 mo | Tumor control 100 |
| Kida *et al*[75], 2000 | 2000 | 12 (total number of patients in the study is 51) | 100 | WHO Grade I low grade astrocytoma | As part of initial management or salvage therapy | GKSRS | Mean margin dose 12.5 Gy | Mean age 9.8 yr | Mean tumor diameter 25.4 mm | - | Mean 27.6 mo | Tumor control 91.7 |
| Boëthius *et al*[76], 2002 | 1978-1997 | 19 | 84.2 | Pilocytic astrocytoma | Adjuvant therapy | GKSRS | Median margin dose 10 Gy | Mean age 10.6 yr (range: 2-60 yr) | Median 2.2 cc | 2 patients | Median radiological follow-up 4.7 yr | Tumor control 94.7 |
| Hadjipanayis *et al*[77], 2003 | 1987-2000 | 49 | 59 | Pilocytic astrocytoma (37 patients) and WHO grade II fibrillary astrocytoma (12 patients) | As part of initial management or salvage therapy | GKSRS | Median margin dose 15 Gy | Median age 14 yr (range: 3-52 yr) for patients with Pilocytic astrocytoma and median age 25 yr (range: 5-57 yr) for patients with WHO Grade II fibrillary astrocytoma | Median 3.3 cc | 13 patients | Median 32 mo after SRS | Tumor control 67 |
| Saran *et al*[78], 2002 | 1994-1999 | 14 | 100 | LGG | As part of initial management or salvage therapy | LINAC-based SRT | Total dose 50-55 Gy | Median age 8 yr (range: 5-16 yr) | Median 19.5 cc | 0 patient | Median 33 mo | PFS 87 at 3 yr |
| Marcus *et al*[79], 2005 | 1992-1998 | 50 | - | WHO Grade I-II astrocytoma | Salvage therapy | LINAC-based SRT | Mean total dose 52.2 Gy | Median age 9 yr (range: 2-26 yr) | ≤ 5 cm in maximal dimension in all patients | 0 patient | Median 6.9 yr | PFS 82.5 at 5 yr, PFS 65 at 8 yr |
| Wang *et al*[80], 2006 | 1993-2003 | 21 | - | LGG | Primary, boost, adjuvant or salvage therapy | GKSRS | Median margin dose 14.5 Gy | Median age 20 yr (range: 6-70 yr) | Median 2.4 cc | 7 patients | Median radiological follow-up 49 mo | Tumor control 67 |
| Kano *et al*[81], 2009 | 1987-2006 | 50 | 100 | Pilocytic astrocytoma | As part of initial management or salvage therapy | GKSRS | Median margin dose 14.5 Gy | Median age 10.5 yr (range: 4.2-17.9 yr) | Median 2.1 cc | 5 patients | Median 55.5 mo | PFS 70.8 at 5 yr |
| Henderson *et al*[82], 2009 | 1997-2004 | 12 | - | WHO Grade I LGG (10 patients), WHO Grade II LGG (2 patients) | As part of initial management or salvage therapy | GKSRS | Median margin dose 13 Gy | Median age 17.4 yr (range: 5.9-63 yr) | Median 4.4 cc | 4 patients | Median 48.2 mo | PFS 75 at 4 yr |
| Weintraub *et al*[83], 2012 | 1989-2011 | 24 | 100 | LGG | As part of initial management or salvage therapy | GKSRS | Median margin dose 15 Gy | Median age 11 yr (range: 4-18 yr) | Mean 2.4 cc | 3 patients | Median imaging follow-up 74 mo | Tumor control 83 |
| Hallemeier *et al*[84], 2012 | 1992-2005 | 18 | 33 | Pilocytic astrocytoma | As part of initial management or salvage therapy | GKSRS | Median margin dose 15 Gy | Median age 23 yr (range: 4-56 yr) | Median 9.1 cc | 10 patients | Median 8 yr | PFS 41 at 5 yr |
| Lizarraga *et al*[85], 2012 | 1995-2010 | 12 | 41.7 | Pilocytic astrocytoma | Salvage therapy | LINAC-based SRS or SRT | Median dose 18.75 Gy for SRS and median dose 50.4 Gy for SRT | Median age 21 yr (range: 5-41 yr) | Median 6.5 cc for SRT and median 1.69 cc for SRS | 0 patient | Median 37.5 mo | PFS 73.3 at long term |
| Simonova *et al*[86], 2016 | 1992-2002 | 25 | 100 | Pilocytic astrocytoma | As part of initial management or salvage therapy | GK-based SRS or SRT | Median margin dose 16 Gy for patients receiving single fraction, median dose 25 Gy for SRT | Median age 13 yr (range: 3-17 yr) | Median 2.7 cc | 2 patients | Median 15 yr | PFS 80 at 10 yr |
| Trifiletti *et al*[87], 2017 | 1990-2015 | 28 | - | Pilocytic astrocytoma | As part of initial management or salvage therapy | GK-based SRS or SRT | Median margin dose 16 Gy | Median age 17.4 yr (range: 2-70.3 yr) | Median 1.84 cc | 4 patients | Median 5.4 yr | PFS 96 at 6 yr |
| Gagliardi *et al*[88], 2017 | 2001-2014 | 39 | 23.8 | LGG | As part of initial management or salvage therapy | GKSRS | Median margin dose 15 Gy | Median age 31 yr (range: 9-72 yr) | Median 1.24 cc | 8 patients | Median 54.5 mo | PFS 52.8 at 5 yr |

LGG: Low grade glioma; SRS: Stereotactic radiosurgery; GKSRS: Gamma knife stereotactic radiosurgery; WHO: World Health Organization; PFS: Progression free survival; LINAC: Linear accelerator; SRT: Stereotactic radiotherapy.