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Editorial Board Member of *World Journal of Methodology*, Rodrigo Valenzuela, PhD, Associated Professor, Department of Nutrition, Faculty of Medicine, University of Chile, Independence Av. 1027, Santiago 8380000, Chile. rvalenzuelab@med.uchile.cl

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MINIREVIEWS

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

Omer Sager, Ferrat Dincoglan, Selcuk Demiral, Bora Uysal, Hakan Gamsiz, Onurhan Colak, Fatih Ozcan, Esin Gundem, Yelda Elcim, Bahar Dirican, Murat Beyzadeoglu

ORCID number: Omer Sager 0000-0001-7866-2598; Ferrat Dincoglan 0000-0002-7668-0976; Selcuk Demiral 0000-0002-3408-0323; Bora Uysal 0000-0002-7288-7005; Hakan Gamsiz 0000-0002-7791-3487; Onurhan Colak 0000-0003-1421-4678; Fatih Ozcan 0000-0002-1965-7067; Esin Gundem 0000-0002-9482-8567; Yelda Elcim 0000-0001-6274-1267; Bahar Dirican 0000-0002-1749-5375; Murat Beyzadeoglu 0000-0003-1035-7209.

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Omer Sager, Ferrat Dincoglan, Selcuk Demiral, Bora Uysal, Hakan Gamsiz, Onurhan Colak, Fatih Ozcan, Esin Gundem, Yelda Elcim, Bahar Dirican, Murat Beyzadeoglu, Department of Radiation Oncology, Gulhane Medical Faculty, University of Health Sciences, Ankara 06018, Turkey

Corresponding author: Omer Sager, MD, Associate Professor, Department of Radiation Oncology, Gulhane Medical Faculty, University of Health Sciences, Gn.Tevfik Saglam Cad, Ankara 06018, Turkey. omersager@gmail.com

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

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pediatric glial neoplasms in light of the literature.

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

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.

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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 ste-reotactic 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]. Never-theless, 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, con-ventional fractionation is common practice owing to lack of superiority of altered fractionation regimens[41-44]. Of note, several series investigated the utility of hypo-fractionated 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, cranio-pharyngiomas, 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, gangliglioma, 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, hypo-thalamus, 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

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.

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.

REFERENCES

1 **Cunningham RM**, Walton MA, Carter PM. The Major Causes of Death in Children and Adolescents in the United States. *N Engl J Med* 2018; **379**: 2468-2475 [PMID: 30575483 DOI: 10.1056/NEJMsr1804754]

2 **Faury D**, Nantel A, Dunn SE, Guiot MC, Haque T, Hauser P, Garami M, Bognár L, Hanzély Z, Liberski PP, Lopez-Aguilar E, Valera ET, Tone LG, Carret AS, Del Maestro RF, Gleave M, Montes JL, Pietsch T, Albrecht S, Jabado N. Molecular profiling identifies prognostic subgroups of pediatric glioblastoma and shows increased YB-1 expression in tumors. *J Clin Oncol* 2007; **25**: 1196-1208 [PMID: 17401009 DOI: 10.1200/JCO.2006.07.8626]

3 **Packer RJ**. Brain tumors in children. *Arch Neurol* 1999; **56**: 421-425 [PMID: 10199329 DOI: 10.1001/archneur.56.4.421]

4 **Blionas A**, Giakoumettis D, Klonou A, Neromyliotis E, Karydakis P, Themistocleous MS. Paediatric gliomas: diagnosis, molecular biology and management. *Ann Transl Med* 2018; **6**: 251 [PMID: 30069453 DOI: 10.21037/atm.2018.05.11]

5 **Collins KL**, Pollack IF. Pediatric Low-Grade Gliomas. *Cancers (Basel)* 2020; **12** [PMID: 32375301 DOI: 10.3390/cancers12051152]

6 **Vanan MI**, Eisenstat DD. Management of high-grade gliomas in the pediatric patient: Past, present, and future. *Neurooncol Pract* 2014; **1**: 145-157 [PMID: 26034626 DOI: 10.1093/nop/npu022]

7 **Peng L**, Yam PP, Yang LS, Sato S, Li CK, Cheung YT. Neurocognitive impairment in Asian childhood cancer survivors: a systematic review. *Cancer Metastasis Rev* 2020; **39**: 27-41 [PMID: 31965433 DOI: 10.1007/s10555-020-09857-y]

8 **Wei C**, Crowne E. The impact of childhood cancer and its treatment on puberty and subsequent hypothalamic pituitary and gonadal function, in both boys and girls. *Best Pract Res Clin Endocrinol Metab* 2019; **33**: 101291 [PMID: 31327697 DOI: 10.1016/j.beem.2019.101291]

9 **Weyl-Ben-Arush M**. The Price of the Successful Treatment of Pediatric Malignancies. *Curr Pediatr Rev* 2017; **13**: 4-7 [PMID: 27978786 DOI: 10.2174/1573396312666161213103558]

10 **Kebudi R**, Ozdemir GN. Secondary Neoplasms in Children Treated for Cancer. *Curr Pediatr Rev* 2017; **13**: 34-41 [PMID: 27848891 DOI: 10.2174/1573396313666161114233135]

11 **Rodriguez FJ**, Vizcaino MA, Lin MT. Recent Advances on the Molecular Pathology of Glial Neoplasms in Children and Adults. *J Mol Diagn* 2016; **18**: 620-634 [PMID: 27444975 DOI: 10.1016/j.jmoldx.2016.05.005]

12 **Bindra RS**, Wolden SL. Advances in Radiation Therapy in Pediatric Neuro-oncology. *J Child Neurol* 2016; **31**: 506-516 [PMID: 26271789 DOI: 10.1177/0883073815597758]

13 **Ludmir EB**, Grosshans DR, Woodhouse KD. Radiotherapy Advances in Pediatric Neuro-Oncology. *Bioengineering (Basel)* 2018; **5** [PMID: 30400370 DOI: 10.3390/bioengineering5040097]

14 **Pollack IF**, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. *J Neurosurg Pediatr* 2019; **23**: 261-273 [PMID: 30835699 DOI: 10.3171/2018.10.PEDS18377]

15 **Dincoglan F**, Sager O, Uysal B, Demiral S, Gamsiz H, Gündem E, Elcim Y, Dirican B, Beyzadeoglu M. Evaluation of hypofractionated stereotactic radiotherapy (HFSRT) to the resection cavity after surgical resection of brain metastases: A single center experience. *Indian J Cancer* 2019; **56**: 202-206 [PMID: 31389381 DOI: 10.4103/ijc.IJC_345_18]

16 **Dincoglan F**, Sager O, Demiral S, Gamsiz H, Uysal B, Onal E, Ekmen A, Dirican B, Beyzadeoglu M. Fractionated stereotactic radiosurgery for locally recurrent brain metastases after failed stereotactic radiosurgery. *Indian J Cancer* 2019; **56**: 151-156 [PMID: 31062735 DOI: 10.4103/ijc.IJC_786_18]

17 **Dincoglan F**, Sager O, Gamsiz H, Uysal B, Demiral S, Oysul K, Sirin S, Caglan A, Beyzadeoglu M. Management of patients with ≥4 brain metastases using stereotactic radiosurgery boost after whole brain irradiation. *Tumori* 2014; **100**: 302-306 [PMID: 25076242 DOI: 10.1700/1578.17210]

18 **Dincoglan F**, Beyzadeoglu M, Sager O, Oysul K, Sirin S, Surenkok S, Gamsiz H, Uysal B, Demiral S, Dirican B. Image-guided positioning in intracranial non-invasive stereotactic radiosurgery for the treatment of brain metastasis. *Tumori* 2012; **98**: 630-635 [PMID: 23235759 DOI: 10.1700/1190.13205]

19 **Dincoglan F**, Beyzadeoglu M, Sager O, Demiral S, Gamsiz H, Uysal B, Ebruli C, Akin M, Oysul K, Sirin S, Dirican B. Management of patients with recurrent glioblastoma using hypofractionated stereotactic radiotherapy. *Tumori* 2015; **101**: 179-184 [PMID: 25791534 DOI: 10.5301/tj.5000236]

20 **Louis DN**, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; **131**: 803-820 [PMID: 27157931 DOI: 10.1007/s00401-016-1545-1]

21 **Bondy ML**, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaum JA, Sadetzki S, Schlehofer B, Tihan T, Wiemels JL, Wrensch M, Buffler PA; Brain Tumor Epidemiology Consortium. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. *Cancer* 2008; **113**: 1953-1968 [PMID: 18798534 DOI: 10.1002/cncr.23741]

22 **Fangusaro J**. Pediatric high grade glioma: a review and update on tumor clinical characteristics and biology. *Front Oncol* 2012; **2**: 105 [PMID: 22937526 DOI: 10.3389/fonc.2012.00105]

23 **Ostrom QT**, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro Oncol* 2019; **21**: v1-v100 [PMID: 31675094 DOI: 10.1093/neuonc/noz150]

24 **Erker C**, Tamrazi B, Poussaint TY, Mueller S, Mata-Mbemba D, Franceschi E, Brandes AA, Rao A, Haworth KB, Wen PY, Goldman S, Vezina G, MacDonald TJ, Dunkel IJ, Morgan PS, Jaspan T, Prados MD, Warren KE. Response assessment in paediatric high-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Lancet Oncol* 2020; **21**: e317-e329 [PMID: 32502458 DOI: 10.1016/S1470-2045(20)30173-X]

25 **Jones C**, Karajannis MA, Jones DTW, Kieran MW, Monje M, Baker SJ, Becher OJ, Cho YJ, Gupta N, Hawkins C, Hargrave D, Haas-Kogan DA, Jabado N, Li XN, Mueller S, Nicolaides T, Packer RJ, Persson AI, Phillips JJ, Simonds EF, Stafford JM, Tang Y, Pfister SM, Weiss WA. Pediatric high-grade glioma: biologically and clinically in need of new thinking. *Neuro Oncol* 2017; **19**: 153-161 [PMID: 27282398 DOI: 10.1093/neuonc/now101]

26 **Baker SJ**, Ellison DW, Gutmann DH. Pediatric gliomas as neurodevelopmental disorders. *Glia* 2016; **64**: 879-895 [PMID: 26638183 DOI: 10.1002/glia.22945]

27 **Tamber MS**, Rutka JT. Pediatric supratentorial high-grade gliomas. *Neurosurg Focus* 2003; **14**: e1 [PMID: 15727422 DOI: 10.3171/foc.2003.14.2.2]

28 **Broniscer A**, Baker SJ, West AN, Fraser MM, Proko E, Kocak M, Dalton J, Zambetti GP, Ellison DW, Kun LE, Gajjar A, Gilbertson RJ, Fuller CE. Clinical and molecular characteristics of malignant transformation of low-grade glioma in children. *J Clin Oncol* 2007; **25**: 682-689 [PMID: 17308273 DOI: 10.1200/JCO.2006.06.8213]

29 **Gupta S**, Mallick S, Benson R, Haresh KP, Julka PK, Rath GK. Extent of surgical resection and adjuvant temozolomide improves survival in pediatric GBM: a single center experience. *Childs Nerv Syst* 2017; **33**: 951-956 [PMID: 28424876 DOI: 10.1007/s00381-017-3381-6]

30 **Bilginer B**, Hanalioglu S, Turk CC, Narin F, Oguz KK, Soylemezoglu F, Akalan N. Is the Knowledge Pertaining to Adult Glioblastomas Enough for Pediatric Cases? *Turk Neurosurg* 2017; **27**: 279-288 [PMID: 27593770 DOI: 10.5137/1019-5149.JTN.15780-15.1]

31 **Adams H**, Adams HH, Jackson C, Rincon-Torroella J, Jallo GI, Quiñones-Hinojosa A. Evaluating extent of resection in pediatric glioblastoma: a multiple propensity score-adjusted population-based analysis. *Childs Nerv Syst* 2016; **32**: 493-503 [PMID: 26767842 DOI: 10.1007/s00381-015-3006-x]

32 **McCrea HJ**, Bander ED, Venn RA, Reiner AS, Iorgulescu JB, Puchi LA, Schaefer PM, Cederquist G, Greenfield JP. Sex, Age, Anatomic Location, and Extent of Resection Influence Outcomes in Children With High-grade Glioma. *Neurosurgery* 2015; **77**: 443-52; discussion 452 [PMID: 26083157 DOI: 10.1227/NEU.0000000000000845]

33 **Yang T**, Temkin N, Barber J, Geyer JR, Leary S, Browd S, Ojemann JG, Ellenbogen RG. Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. *World Neurosurg* 2013; **79**: 537-544 [PMID: 23017588 DOI: 10.1016/j.wneu.2012.09.015]

34 **Wisoff JH**, Boyett JM, Berger MS, Brant C, Li H, Yates AJ, McGuire-Cullen P, Turski PA, Sutton LN, Allen JC, Packer RJ, Finlay JL. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. *J Neurosurg* 1998; **89**: 52-59 [PMID: 9647172 DOI: 10.3171/jns.1998.89.1.0052]

35 **Broniscer A**, Gajjar A. Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist. *Oncologist* 2004; **9**: 197-206 [PMID: 15047924 DOI: 10.1634/theoncologist.9-2-197]

36 **Fangusaro J**. Pediatric high-grade gliomas and diffuse intrinsic pontine gliomas. *J Child Neurol* 2009; **24**: 1409-1417 [PMID: 19638636 DOI: 10.1177/0883073809338960]

37 **Espiritu AI**, Terencio BB, Jamora RDG. Congenital Glioblastoma Multiforme with Long-Term Childhood Survival: A Case Report and Systematic Review. *World Neurosurg* 2020; **139**: 90-96 [PMID: 32298818 DOI: 10.1016/j.wneu.2020.03.212]

38 **El-Ayadi M**, Ansari M, Sturm D, Gielen GH, Warmuth-Metz M, Kramm CM, von Bueren AO. High-grade glioma in very young children: a rare and particular patient population. *Oncotarget* 2017; **8**: 64564-64578 [PMID: 28969094 DOI: 10.18632/oncotarget.18478]

39 **Dufour C**, Grill J, Lellouch-Tubiana A, Puget S, Chastagner P, Frappaz D, Doz F, Pichon F, Plantaz D, Gentet JC, Raquin MA, Kalifa C. High-grade glioma in children under 5 years of age: a chemotherapy only approach with the BBSFOP protocol. *Eur J Cancer* 2006; **42**: 2939-2945 [PMID: 16962317 DOI: 10.1016/j.ejca.2006.06.021]

40 **Liu M**, Thakkar JP, Garcia CR, Dolecek TA, Wagner LM, Dressler EVM, Villano JL. National cancer database analysis of outcomes in pediatric glioblastoma. *Cancer Med* 2018; **7**: 1151-1159 [PMID: 29532996 DOI: 10.1002/cam4.1404]

41 **Mandell LR**, Kadota R, Freeman C, Douglass EC, Fontanesi J, Cohen ME, Kovnar E, Burger P, Sanford RA, Kepner J, Friedman H, Kun LE. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; **43**: 959-964 [PMID: 10192340 DOI: 10.1016/s0360-3016(98)00501-x]

42 **Fallai C**, Olmi P. Hyperfractionated and accelerated radiation therapy in central nervous system tumors (malignant gliomas, pediatric tumors, and brain metastases). *Radiother Oncol* 1997; **43**: 235-246 [PMID: 9215782 DOI: 10.1016/s0167-8140(96)01897-x]

43 **Freeman CR**, Krischer JP, Sanford RA, Cohen ME, Burger PC, del Carpio R, Halperin EC, Munoz L, Friedman HS, Kun LE. Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children: a Pediatric Oncology Group study. *Int J Radiat Oncol Biol Phys* 1993; **27**: 197-206 [PMID: 8407392 DOI: 10.1016/0360-3016(93)90228-n]

44 **Gallitto M**, Lazarev S, Wasserman I, Stafford JM, Wolden SL, Terezakis SA, Bindra RS, Bakst RL. Role of Radiation Therapy in the Management of Diffuse Intrinsic Pontine Glioma: A Systematic Review. *Adv Radiat Oncol* 2019; **4**: 520-531 [PMID: 31360809 DOI: 10.1016/j.adro.2019.03.009]

45 **Negretti L**, Bouchireb K, Levy-Piedbois C, Habrand JL, Dhermain F, Kalifa C, Grill J, Dufour C. Hypofractionated radiotherapy in the treatment of diffuse intrinsic pontine glioma in children: a single institution's experience. *J Neurooncol* 2011; **104**: 773-777 [PMID: 21327862 DOI: 10.1007/s11060-011-0542-4]

46 **Janssens GO**, Jansen MH, Lauwers SJ, Nowak PJ, Oldenburger FR, Bouffet E, Saran F, Kamphuis-van Ulzen K, van Lindert EJ, Schieving JH, Boterberg T, Kaspers GJ, Span PN, Kaanders JH, Gidding CE, Hargrave D. Hypofractionation *vs* conventional radiation therapy for newly diagnosed diffuse intrinsic pontine glioma: a matched-cohort analysis. *Int J Radiat Oncol Biol Phys* 2013; **85**: 315-320 [PMID: 22682807 DOI: 10.1016/j.ijrobp.2012.04.006]

47 **Zaghloul MS**, Eldebawy E, Ahmed S, Mousa AG, Amin A, Refaat A, Zaky I, Elkhateeb N, Sabry M. Hypofractionated conformal radiotherapy for pediatric diffuse intrinsic pontine glioma (DIPG): a randomized controlled trial. *Radiother Oncol* 2014; **111**: 35-40 [PMID: 24560760 DOI: 10.1016/j.radonc.2014.01.013]

48 **Shah JL**, Li G, Shaffer JL, Azoulay MI, Gibbs IC, Nagpal S, Soltys SG. Stereotactic Radiosurgery and Hypofractionated Radiotherapy for Glioblastoma. *Neurosurgery* 2018; **82**: 24-34 [PMID: 28605463 DOI: 10.1093/neuros/nyx115]

49 **Prisco FE**, Weltman E, de Hanriot RM, Brandt RA. Radiosurgical boost for primary high-grade gliomas. *J Neurooncol* 2002; **57**: 151-160 [PMID: 12125977 DOI: 10.1023/a:1015757322379]

50 **Gannett D**, Stea B, Lulu B, Adair T, Verdi C, Hamilton A. Stereotactic radiosurgery as an adjunct to surgery and external beam radiotherapy in the treatment of patients with malignant gliomas. *Int J Radiat Oncol Biol Phys* 1995; **33**: 461-468 [PMID: 7673034 DOI: 10.1016/0360-3016(95)00087-F]

51 **Loeffler JS**, Alexander E 3rd, Shea WM, Wen PY, Fine HA, Kooy HM, Black PM. Radiosurgery as part of the initial management of patients with malignant gliomas. *J Clin Oncol* 1992; **10**: 1379-1385 [PMID: 1325539 DOI: 10.1200/JCO.1992.10.9.1379]

52 **Trone JC**, Vallard A, Sotton S, Ben Mrad M, Jmour O, Magné N, Pommier B, Laporte S, Ollier E. Survival after hypofractionation in glioblastoma: a systematic review and meta-analysis. *Radiat Oncol* 2020; **15**: 145 [PMID: 32513205 DOI: 10.1186/s13014-020-01584-6]

53 **Souhami L**, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran WJ Jr. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys* 2004; **60**: 853-860 [PMID: 15465203 DOI: 10.1016/j.ijrobp.2004.04.011]

54 **Lipani JD**, Jackson PS, Soltys SG, Sato K, Adler JR. Survival following CyberKnife radiosurgery and hypofractionated radiotherapy for newly diagnosed glioblastoma multiforme. *Technol Cancer Res Treat* 2008; **7**: 249-255 [PMID: 18473497 DOI: 10.1177/153303460800700311]

55 **Hsieh PC**, Chandler JP, Bhangoo S, Panagiotopoulos K, Kalapurakal JA, Marymont MH, Cozzens JW, Levy RM, Salehi S. Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery* 2005; **57**: 684-92; discussion 684 [PMID: 16239880 DOI: 10.1093/neurosurgery/57.4.684]

56 **Nwokedi EC**, DiBiase SJ, Jabbour S, Herman J, Amin P, Chin LS. Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. *Neurosurgery* 2002; **50**: 41-6; discussion 46 [PMID: 11844233 DOI: 10.1097/00006123-200201000-00009]

57 **Fuchs I**, Kreil W, Sutter B, Papaethymiou G, Pendl G. Gamma Knife radiosurgery of brainstem gliomas. *Acta Neurochir Suppl* 2002; **84**: 85-90 [PMID: 12379009 DOI: 10.1007/978-3-7091-6117-3_10]

58 **Giller CA**, Berger BD, Pistenmaa DA, Sklar F, Weprin B, Shapiro K, Winick N, Mulne AF, Delp JL, Gilio JP, Gall KP, Dicke KA, Swift D, Sacco D, Harris-Henderson K, Bowers D. Robotically guided radiosurgery for children. *Pediatr Blood Cancer* 2005; **45**: 304-310 [PMID: 15558704 DOI: 10.1002/pbc.20267]

59 **Hodgson DC**, Goumnerova LC, Loeffler JS, Dutton S, Black PM, Alexander E 3rd, Xu R, Kooy H, Silver B, Tarbell NJ. Radiosurgery in the management of pediatric brain tumors. *Int J Radiat Oncol Biol Phys* 2001; **50**: 929-935 [PMID: 11429220 DOI: 10.1016/s0360-3016(01)01518-8]

60 **Baumann GS**, Wara WM, Larson DA, Sneed PK, Gutin PH, Ciricillo SF, McDermott MW, Park E, Stalpers LJ, Verhey LJ, Smith V, Petti PL, Edwards MS. Gamma knife radiosurgery in children. *Pediatr Neurosurg* 1996; **24**: 193-201 [PMID: 8873161 DOI: 10.1159/000121037]

61 **Grabb PA**, Lunsford LD, Albright AL, Kondziolka D, Flickinger JC. Stereotactic radiosurgery for glial neoplasms of childhood. *Neurosurgery* 1996; **38**: 696-701; discussion 701 [PMID: 8692387 DOI: 10.1227/00006123-199604000-00013]

62 **Krishnatry R**, Zhukova N, Guerreiro Stucklin AS, Pole JD, Mistry M, Fried I, Ramaswamy V, Bartels U, Huang A, Laperriere N, Dirks P, Nathan PC, Greenberg M, Malkin D, Hawkins C, Bandopadhayay P, Kieran MW, Manley PE, Bouffet E, Tabori U. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: A population-based study. *Cancer* 2016; **122**: 1261-1269 [PMID: 26970559 DOI: 10.1002/cncr.29907]

63 **Bandopadhayay P**, Bergthold G, London WB, Goumnerova LC, Morales La Madrid A, Marcus KJ, Guo D, Ullrich NJ, Robison NJ, Chi SN, Beroukhim R, Kieran MW, Manley PE. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. *Pediatr Blood Cancer* 2014; **61**: 1173-1179 [PMID: 24482038 DOI: 10.1002/pbc.24958]

64 **Watson GA**, Kadota RP, Wisoff JH. Multidisciplinary management of pediatric low-grade gliomas. *Semin Radiat Oncol* 2001; **11**: 152-162 [PMID: 11285553 DOI: 10.1053/srao.2001.21421]

65 **de Blank P**, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. *Curr Opin Pediatr* 2019; **31**: 21-27 [PMID: 30531227 DOI: 10.1097/MOP.0000000000000717]

66 **Shibamoto Y**, Kitakabu Y, Takahashi M, Yamashita J, Oda Y, Kikuchi H, Abe M. Supratentorial low-grade astrocytoma. Correlation of computed tomography findings with effect of radiation therapy and prognostic variables. *Cancer* 1993; **72**: 190-195 [PMID: 8508405 DOI: 10.1002/1097-0142(19930701)72:1<190::aid-cncr2820720134>3.0.co;2-y]

67 **Shaw EG**, Daumas-Duport C, Scheithauer BW, Gilbertson DT, O'Fallon JR, Earle JD, Laws ER Jr, Okazaki H. Radiation therapy in the management of low-grade supratentorial astrocytomas. *J Neurosurg* 1989; **70**: 853-861 [PMID: 2715812 DOI: 10.3171/jns.1989.70.6.0853]

68 **Aloi D**, Belgioia L, Barra S, Giannelli F, Cavagnetto F, Gallo F, Milanaccio C, Garrè M, Di Profio S, Di Iorgi N, Corvò R. Neuroendocrine late effects after tailored photon radiotherapy for children with low grade gliomas: Long term correlation with tumour and treatment parameters. *Radiother Oncol* 2017; **125**: 241-247 [PMID: 29037775 DOI: 10.1016/j.radonc.2017.09.034]

69 **Indelicato DJ**, Rotondo RL, Uezono H, Sandler ES, Aldana PR, Ranalli NJ, Beier AD, Morris CG, Bradley JA. Outcomes Following Proton Therapy for Pediatric Low-Grade Glioma. *Int J Radiat Oncol Biol Phys* 2019; **104**: 149-156 [PMID: 30684665 DOI: 10.1016/j.ijrobp.2019.01.078]

70 **Müller K**, Gnekow A, Falkenstein F, Scheiderbauer J, Zwiener I, Pietsch T, Warmuth-Metz M, Voges J, Nikkhah G, Flentje M, Combs SE, Vordermark D, Kocher M, Kortmann RD. Radiotherapy in pediatric pilocytic astrocytomas. A subgroup analysis within the prospective multicenter study HIT-LGG 1996 by the German Society of Pediatric Oncology and Hematology (GPOH). *Strahlenther Onkol* 2013; **189**: 647-655 [PMID: 23831852 DOI: 10.1007/s00066-013-0357-7]

71 **Huynh-Le MP**, Walker AJ, Burger PC, Jallo GI, Cohen KJ, Wharam MD, Terezakis SA. Management of pediatric intracranial low-grade gliomas: long-term follow-up after radiation therapy. *Childs Nerv Syst* 2016; **32**: 1425-1430 [PMID: 27179530 DOI: 10.1007/s00381-016-3100-8]

72 **Cherlow JM**, Shaw DWW, Margraf LR, Bowers DC, Huang J, Fouladi M, Onar-Thomas A, Zhou T, Pollack IF, Gajjar A, Kessel SK, Cullen PL, McMullen K, Wellons JC, Merchant TE. Conformal Radiation Therapy for Pediatric Patients with Low-Grade Glioma: Results from the Children's Oncology Group Phase 2 Study ACNS0221. *Int J Radiat Oncol Biol Phys* 2019; **103**: 861-868 [PMID: 30419305 DOI: 10.1016/j.ijrobp.2018.11.004]

73 **Barcia JA**, Barcia-Salorio JL, Ferrer C, Ferrer E, Algás R, Hernández G. Stereotactic radiosurgery of deeply seated low grade gliomas. *Acta Neurochir Suppl* 1994; **62**: 58-61 [PMID: 7717138 DOI: 10.1007/978-3-7091-9371-6_12]

74 **Somaza SC**, Kondziolka D, Lunsford LD, Flickinger JC, Bissonette DJ, Albright AL. Early outcomes after stereotactic radiosurgery for growing pilocytic astrocytomas in children. *Pediatr Neurosurg* 1996; **25**: 109-115 [PMID: 9144708 DOI: 10.1159/000121107]

75 **Kida Y**, Kobayashi T, Mori Y. Gamma knife radiosurgery for low-grade astrocytomas: results of long-term follow up. *J Neurosurg* 2000; **93** Suppl 3: 42-46 [PMID: 11143261 DOI:

10.3171/jns.2000.93.supplement_3.0042]
76 **Boëthius J**, Ulfarsson E, Rähn T, Lippittz B. Gamma knife radiosurgery for pilocytic astrocytomas. *J Neurosurg* 2002; **97**: 677-680 [PMID: 12507119 DOI: 10.3171/jns.2002.97.supplement_5.0677]
77 **Hadjipanayis CG**, Kondziolka D, Flickinger JC, Lunsford LD. The role of stereotactic radiosurgery for low-grade astrocytomas. *Neurosurg Focus* 2003; **14**: e15 [PMID: 15669811 DOI: 10.3171/foc.2003.14.5.16]
78 **Saran FH**, Baumert BG, Khoo VS, Adams EJ, Garré ML, Warrington AP, Brada M. Stereotactically guided conformal radiotherapy for progressive low-grade gliomas of childhood. *Int J Radiat Oncol Biol Phys* 2002; **53**: 43-51 [PMID: 12007940 DOI: 10.1016/s0360-3016(02)02734-7]
79 **Marcus KJ**, Goumnerova L, Billett AL, Lavally B, Scott RM, Bishop K, Xu R, Young Poussaint T, Kieran M, Kooy H, Pomeroy SL, Tarbell NJ. Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. *Int J Radiat Oncol Biol Phys* 2005; **61**: 374-379 [PMID: 15667955 DOI: 10.1016/j.ijrobp.2004.06.012]
80 **Wang LW**, Shiau CY, Chung WY, Wu HM, Guo WY, Liu KD, Ho DM, Wong TT, Pan DH. Gamma Knife surgery for low-grade astrocytomas: evaluation of long-term outcome based on a 10-year experience. *J Neurosurg* 2006; **105** Suppl: 127-132 [PMID: 18503345 DOI: 10.3171/sup.2006.105.7.127]
81 **Kano H**, Niranjan A, Kondziolka D, Flickinger JC, Pollack IF, Jakacki RI, Lunsford LD. Stereotactic radiosurgery for pilocytic astrocytomas part 2: outcomes in pediatric patients. *J Neurooncol* 2009; **95**: 219-229 [PMID: 19468692 DOI: 10.1007/s11060-009-9912-6]
82 **Henderson MA**, Fakiris AJ, Timmerman RD, Worth RM, Lo SS, Witt TC. Gamma knife stereotactic radiosurgery for low-grade astrocytomas. *Stereotact Funct Neurosurg* 2009; **87**: 161-167 [PMID: 19321969 DOI: 10.1159/000209297]
83 **Weintraub D**, Yen CP, Xu Z, Savage J, Williams B, Sheehan J. Gamma knife surgery of pediatric gliomas. *J Neurosurg Pediatr* 2012; **10**: 471-477 [PMID: 23061823 DOI: 10.3171/2012.9.PEDS12257]
84 **Hallemeier CL**, Pollock BE, Schomberg PJ, Link MJ, Brown PD, Stafford SL. Stereotactic radiosurgery for recurrent or unresectable pilocytic astrocytoma. *Int J Radiat Oncol Biol Phys* 2012; **83**: 107-112 [PMID: 22019245 DOI: 10.1016/j.ijrobp.2011.05.038]
85 **Lizarraga KJ**, Gorgulho A, Lee SP, Rauscher G, Selch MT, DeSalles AA. Stereotactic radiation therapy for progressive residual pilocytic astrocytomas. *J Neurooncol* 2012; **109**: 129-135 [PMID: 22644536 DOI: 10.1007/s11060-012-0877-5]
86 **Simonova G**, Kozubikova P, Liscak R, Novotny J Jr. Leksell Gamma Knife treatment for pilocytic astrocytomas: long-term results. *J Neurosurg Pediatr* 2016; **18**: 58-64 [PMID: 26991883 DOI: 10.3171/2015.10.PEDS14443]
87 **Trifiletti DM**, Peach MS, Xu Z, Kersh R, Showalter TN, Sheehan JP. Evaluation of outcomes after stereotactic radiosurgery for pilocytic astrocytoma. *J Neurooncol* 2017; **134**: 297-302 [PMID: 28567590 DOI: 10.1007/s11060-017-2521-x]
88 **Gagliardi F**, Bailo M, Spina A, Donofrio CA, Boari N, Franzin A, Fava A, Del Vecchio A, Bolognesi A, Mortini P. Gamma Knife Radiosurgery for Low-Grade Gliomas: Clinical Results at Long-Term Follow-Up of Tumor Control and Patients' Quality of Life. *World Neurosurg* 2017; **101**: 540-553 [PMID: 28216397 DOI: 10.1016/j.wneu.2017.02.041]
89 **Mohamad O**, Wardak Z, Bowers DC, Le AH, Dan T, Abdulrahman R, Gargan L, Klesse L, Weprin B, Swift D, Price A, Ding C, Stojadinovic S, Sklar F, Braga B, Timmerman R. Margin-Free Fractionated Stereotactic Radiation Therapy for Pediatric Brain Tumors. *Pract Radiat Oncol* 2020; **10**: e485-e494 [PMID: 32428764 DOI: 10.1016/j.prro.2020.03.013]
90 **Duke ES**, Packer RJ. Update on Pediatric Brain Tumors: the Molecular Era and Neuro-immunologic Beginnings. *Curr Neurol Neurosci Rep* 2020; **20**: 30 [PMID: 32564169 DOI: 10.1007/s11910-020-01050-6]
91 **Foster JB**, Madsen PJ, Hegde M, Ahmed N, Cole KA, Maris JM, Resnick AC, Storm PB, Waanders AJ. Immunotherapy for pediatric brain tumors: past and present. *Neuro Oncol* 2019; **21**: 1226-1238 [PMID: 31504801 DOI: 10.1093/neuonc/noz077]
92 **Wang SS**, Bandopadhayay P, Jenkins MR. Towards Immunotherapy for Pediatric Brain Tumors. *Trends Immunol* 2019; **40**: 748-761 [PMID: 31229353 DOI: 10.1016/j.it.2019.05.009]
93 **Sayour EJ**, Mitchell DA. Immunotherapy for Pediatric Brain Tumors. *Brain Sci* 2017; **7** [PMID: 29065490 DOI: 10.3390/brainsci7100137]

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