NEUROLOGY INDIA
Publication of the Neurological Society of India

REVIEW ARTICLE
Year : 2020 | **Volume** : 68 | **Issue** : 2 | **Page** : 290--298

Role of Gamma Knife Radiosurgery in the Management of Intracranial Gliomas

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Abstract

Gamma knife for gliomas is a relatively obscure treatment modality with few reports and small series available on the same. An extensive search of English Language literature yields no comprehensive reviews of the same. We here, attempt to review the available literature on gamma knife for all types of gliomas: Low grade, High grade, recurrent, and also for pediatric populations. We used keywords such as "Gamma Knife Glioma," "Stereotactic Radiosurgery Glioma," "Gamma Knife," "Adjuvant therapy Glioma" "Recurrent Glioma" on PubMed search engine, and articles were selected with respect to their use of gamma Knife for Gliomas and outcome for the same. These were then analyzed and salient findings were elucidated. This was combined with National Comprehensive Cancer Network guidelines for the same and also included our own initial experience with these tumors. Gamma-knife improved long term survival and quality of life in patients with low grade gliomas. In pediatric low grade gliomas, it may be considered as a treatment modality with a marginal dose of 12–14 Gy, especially in eloquent structures such as brain stem glioma, anterior optic pathway hypothalamic glioma. However, in newly diagnosed high-grade glioma gamma knife radiosurgery (GKRS) is not recommended because of a lack of definitive evidence in tumor control and quality of life. GKRS may find its role in palliative care of recurrent gliomas irrespective of type and grade. Inspite of growing experience with GKRS for gliomas, there is no Level I evidence in support of GKRS, hence better designed randomized controlled trials with long term outcomes are warranted. Although this modality is not a "one size fits all' therapy, it has its moments when chosen correctly and applied wisely. Gliomas being the most common tumors operated in any neurosurgical setting, knowledge about this modality and its application is essential and useful.

How to cite this article:
Deora H, Tripathi M, Tewari MK, Ahuja CK, Kumar N, Kaur A, Kamboj P. Role of Gamma Knife Radiosurgery in the Management of Intracranial Gliomas.Neurol India 2020;68:290-298

How to cite this URL:
Deora H, Tripathi M, Tewari MK, Ahuja CK, Kumar N, Kaur A, Kamboj P. Role of Gamma Knife Radiosurgery in the Management of Intracranial Gliomas. Neurol India [serial online] 2020 [cited 2020 Jun 11];68:290-298
Available from: http://www.neurologyindia.com/text.asp?2020/68/2/290/284356

Full Text

Gamma knife radiosurgery (GKRS) is an established treatment modality for a wide spectrum of lesions including benign and malignant intracranial pathologies. It can be applied as a single fraction as in stereotactic radiosurgery (SRS), or as fractionated stereotactic radiotherapy in which multiple fractions (2–5) are administered over a period of 2–4 weeks.[1] In spite the implementation of increasingly aggressive surgery, chemotherapy, and fractionated radiotherapy for the treatment of gliomas, most therapeutic regimens have resulted in only modest improvements in patient survival. Adding to the misery is the fact that high-grade gliomas (HGGs) are the most common type of malignant, primary brain tumor that comprises 35–45% of all primary brain tumors in a adult population.[1] Surgical decompression remains the first line therapy but may be limited in cases when either the tumor is in an eloquent area or with local or distant recurrence, posing a challenging dilemma for the treating team. In this chapter, we will review the evolving trend of GKRS for gliomas and its implications.

A Brief History of Gamma Knife Radiosurgery

Prof. Lars Leksell developed GKRS in the late 1960s. It was initially conceived as an alternative to open stereotactic lesioning for functional neurosurgery but has since become a tool that is currently being used as primary and adjuvant therapy for many intracranial pathologies. GKRS does not follow the conventional 5R's (repair, redistribution, repopulation, reoxygenation, and radiosensitivity) of radiotherapy. It is not according to variable tissue response to fractionated radiation. Irrespective of radiosensitivity, it provides a high control over the targeted volume, as it does not depend on the stage of a cell cycle for radiation to impart its effect. It delivers a high dose of radiation in a single/multiple session to a stereotactically defined target by converging multiple beams of ionizing radiation. The chances of collateral damage by radiation to the neighboring structures are minimized by virtue of rapid dose fall out, high precision, and conformity offered by the advanced versions of the gamma knife machine (Leksell Perfexion and ICON model) and planning software while maintaining good target control.[2]

Radiobiology of Gliomas

Gliomas conventionally contain a proportion of hypoxic cells, which are often resistant to damage by radiation therapy.[3] After irradiation of these cells, there appears to be a point in their life cycle when the accumulation of sublethal insults at low doses imparts a cumulative effect. Although many theories are postulated for the same, this appears to be the result of DNA being a target for cellular damage by ionizing radiation, and the resultant double-stranded breaks causing the cell-cycle arrest and cell death. After a single dose of radiation therapy, there is a decrease in cell viability, as high as 2.5–3 times. Oxygenated cells are highly susceptible to radiation as compared to hypoxic cells and dominate the response to radiation. Thus, GKRS takes advantage of the natural difference in susceptibility of pathological and normal tissues. The relative radio-resistance of normal brain tissue relates to its low mitotic activity and the ability for cellular repair.

The linear-quadratic (LQ) model has been used to compute the effects of ionization radiation on normal and neoplastic cells. It also calculates iso-effect doses among different therapeutic regimens and calculates tumor cell kill rate. GKRS allows delivery of high doses of precise radiation, with a steep dose fall-off to a defined target during one procedure to provide a powerful radiobiological effect. This allows sparing more normal tissue such as surrounding brain. The alpha-beta ratio (α/β ratio) is a critical concept in this regard. It is according to preclinical and clinical data and is considered ~ 2 for tissue in the central nervous system (CNS), 3 for late-responding tissues, and 10 for early responding tissues. The α/β ratio is necessary when calculating the LQ equation to

determine the dose equivalent to a conventional radiotherapy regimen. These ratios can then be used to help regulate the dose for tumor control while minimizing normal tissue toxicity. Although specific ratios have been defined, it is useful to remember that malignant tumors such as brain metastases and primary malignant brain tumors have higher α/β ratios, estimated to be closer to 10, typical of early responding tissues. It is in contrast to slow-growing benign pathologies such as pituitary adenomas, arteriovenous malformations, and meningiomas, which have lower α/β ratios, estimated to be closer to 3 and representative of late responding tissues. Notwithstanding of the ambiguities of the true α/β ratios of all tumors, particularly in the brain, the overall goal of SRS is to deliver highly conformal treatment with radiation to the tumor while sparing normal tissue surrounding the target volume.[4]

Variations in dose rates also carry an importance. Higher dose rate (the same total dose delivered over a shorter period of time or a larger dose in an equivalent amount of time) increases the lethality of a dose owing to greater interference with intrinsic cellular repair mechanisms during irradiation. Threshold dose rates of 1 Gy/min intensify this effect.[4] This implies that in GKRS, the normal tissue surrounding a target not only receives a markedly lower dose but also receives it at a lower dose rate.[5] There are two core concepts that need to be understood with respect to dosing in GKRS- Dose (hypofractionation) fractionation and volume fractionation. In the hypofractionation technique, the total radiation dose is delivered to the target in 4 or 5 fractionations (hypofractionation) on consecutive or alternate day regimen. In the volume fractionation technique, a large target is divided into smaller volume targets and full radiation dose is delivered to each of these small targets spaced over a few months. Potential advantages of fractionation are lesser radiation damage to normal brain parenchyma while maintaining the dose delivered to the lesion. The most critical aspect of preventing radiation damage to surrounding brain during any radiosurgery procedure is to keep the radiation exposure to the surrounding normal brain to the bare minimum. To achieve this, the "volume of normal brain receiving 12 G"' should be adopted as a standard baseline value and this volume should be kept less than 10 cc.[5]

Abscopal Effect and Two-Target Theory

Radiation has well-documented and characterized direct cytotoxic effects on the cells and tissues, but recently, there has been considerable evidence regarding the unpredictable systemic effects of radiation such as the inhibition of distant tumor growth, called the abscopal effect and also enhanced the growth of distant metastasis.[6] Combination of Radiotherapy (RT) and immune checkpoint inhibitors has shown systemic antitumor responses. This abscopal effect was first reported by Mole in 1953, has only recently been proven to be T cell-dependent, and is caused by activation of p53, reactive oxygen species, and cytokines including IL-6, IL-1a, and TNF-a. This is in addition to the bystander effect, which is radiation-induced non-targeted effects in non-irradiated cells within or nearby an irradiated volume and is considered to be because of the activation of p53, reactive oxygen species, and cytokines including TGF-b1 and TNF-a.

To prove this theory, Golden et al.[7] enrolled 41 patients with stable or progressing disease at atleast three sites who were being maintained on previous standard systemic regimen and granulocyte-macrophage colony-stimulating factor. They then received fractionated irradiation (3.5 Gy × 10 daily fractions) in one lesion with the non-irradiated lesion tested at 7–8 weeks by CT to look for a reduction in size (atleast 30%). In total, 27% cases demonstrated responses and also had a survival advantage (21 vs. 8 months). They postulated that this effect was mediated by immunogenic tumor cell death involving dendritic cells, T regulatory cells, and suppressor cells. The ultimate ambition was to allow radiotherapy to act with a "Two-Target" principle: One within the irradiated field and one distant to it.

Pathophysiological Effects of Gamma Knife

As radiobiological effects of radiation were being understood, there was a need to understand its impact on normal brain tissues. Thus, the effect of a single dose of GKRS on the normal parietal lobe of rats was studied. A single dose of 50 Gy caused astrocyte swelling and fibrin deposition in capillary walls without changes in neuronal morphology or breakdown of the blood-brain barrier (BBB) at 12 months. At 75 Gy, more vigorous morphological changes were noted in astrocytes within 4 months. In addition, necrosis, breakdown of the BBB, and hemispheric swelling were noted. At 120 Gy, astrocyte swelling occurred within one week of irradiation, and necrosis was seen at four weeks, but it was not associated with hemispheric edema.[8]

It is now an accepted fact that the effect of GKRS is owing to radiation-induced DNA damage. Other postulated mechanisms include microvascular damage, which has been demonstrated in the blood supply of meningioma and obliteration of nidus in arteriovenous malformations.[9] Reduction in blood flow is considered to be an early marker of response. Other postulated mechanism is apoptosis of cells, especially rapidly dividing ones.[10] All this is delivered in a single session, which improves the effectiveness of the target dose, by 2.5 to 3 times that of the same dose delivered in a fractionated manner. There is, however, no necrosis involved in the action of GKRS. This is owing to the fact that the dose used in clinical practice is far too less to cause necrosis.

In principle, GKRS is a modality with inhomogeneous radiation distribution i.e. the dose distribution varies from the prescribed marginal dose to the maximum dose from the periphery to center in an inhomogeneous pattern. "Hot spots" are the areas of local maximal distribution of radiation often owing to overlapping effects of many radiation shots, which causes the radiation dose distribution, to become inhomogeneous. Historically, it remained one of the major criticisms against GKRS, which was later refuted with long-term follow-up results in various intracranial pathologies. This result in islands of lethally injured cells that might enhance the cell kill in sublethal injury zones. Cells that are sublethally injured in the vicinity of lethally injured cells are thus more likely to undergo apoptosis than sublethally injured cells in the vicinity of other sublethally injured cells. Ideally, the distribution of isocenters should be such that the hot spot lies in the center of the lesion. It would thus cover the most hypoxic and hence resistant area to radiation.[11]

Low-Grade Gliomas

Low-grade gliomas (LGG) are defined as WHO grade I and II tumors. It accounts for approximately 15% of primary tumors of the CNS in adults and predominantly comprises pilocytic astrocytoma, diffuse grade 2 astrocytoma, and oligodendrogliomas.[12] Ideally, they should not be considered under a blanket term, as oligodendroglioma has a different natural history in comparison to other LGG. These tumors pose a threat, as they tend to occur in the pediatric and young adult populations. Grade 1 lesions often follow a benign course following surgical excision, whereas grade 2 gliomas invariably progress, either through recurrence or dedifferentiation into a higher-grade neoplasm. There are currently many treatment options available for Low Grade Glioma (LGG) (surgery, radiation, chemotherapy, etc.), and microsurgical gross total resection remains the treatment of choice whenever feasible. Other options include biopsy and monitoring with serial imaging, surgical resection, radiotherapy- either neo or adjuvant, chemotherapy, and SRS (as a standalone or boost treatment option). There is no class I evidence in support of these treatment modalities, as it is difficult to obtain. The reasons are a relatively slow rate of lesion progression, which will necessitate a large cohort and long follow-up period that is difficult in the majority of cases owing to medical and ethical concerns.[13],[14] The predominance in young population along with ultimately dismal prognosis raises alarming questions for better results and treatment modalities. Although the survival rates have improved recently with 5-year survivals of approximately 60% and 10-year survivals of approximately 40%, this improvement is probably owing to earlier diagnosis with the advent of better imaging tools.[12]

There are a number of small studies demonstrating the efficacy of GKRS on LGGs, but data regarding the long-term efficacy of GKRS on a large number of patients with LGG is lacking [Table 1]. For pilocytic astrocytomas, gross total resection is the treatment of choice, and role of GKRS is limited to focal brain stem gliomas, optic

pathway hypothalamic gliomas, and remnants in peduncular locations. GKRS was generally performed for tumors in eloquent areas, residual tumor, or late progression after surgery. Heppner et al.[15] did a retrospective review of 49 patients treated between 1989 and 2003 with a median follow-up period of 63 months. Median clinical progression-free survival was 44 months, and median radiological progression-free survival was 37 months. Five-year radiological progression-free survival was 37%, and clinical progression-free survival was 41%. Mortality due to tumor progression occurred in 7 patients (14%). Complete radiological remission was seen in 14 patients (29%). Complications were minimal, seen in 4 patients (8%). Of these, two resolved without sequelae, one required surgery for neurological decline and associated radiation-induced changes, and one patient suffered a permanent neurological deficit from treatment. All the tumors had either undergone a biopsy or surgical decompression before the treatment. Majority of the cases were grade 2 gliomas and pilocytic tumors, and there were no statistically different outcomes between them.{Table 1}

Barcia et al. studied the effects of radiosurgery in 16 patients with low-grade gliomas.[16] Six of these cases had received conventional external fractionated radiotherapy, and another six patients with tumors less than 5 cm in diameter, receive Stereotactic radiosurgery (SRS). In this study, tumors disappeared in eight cases and significantly decreased in size or ceased growth in five cases. Unfortunately, survival was not reported in this study. Pittsburgh group has also reported their experience with patients of pilocytic astrocytoma with long-term follow-up. GKRS provided long-term tumor control rate to the extent of 68% in solid-cystic tumors, whereas 84% with the predominant solid component. Factors associated with poor control were an older age group, cystic components, previous failed fractionated radiation, and diffuse tumors. The dose range for a consistent good outcome was 15 Gy.[17] The timing of treatment is another important prognostic factor. The lesions receiving GKRS as an early treatment for the residual tumor after surgical decompression results in better tumor control in comparison to the treatment for the residual lesion following earlier treatment modalities such as surgery, radiation therapy, or chemotherapy. Brain stem gliomas have a dismal prognosis and had a shorter progression-free survival. This could be secondary to lesser radiation dose with respect to the vicinity of the brain stem. There are anecdotal case reports of spontaneous regression of pilocytic astrocytomas but are almost associated with a visual pathway or occur in patients with neurofibromatosis I. In patients of recurrent grade 2 oligodendroglia, the tumor grade and target volume were the two deciding parameters for long-term survival.

There appears to be a low rate of complications with this therapy as evidenced by this study. However, GKRS can turn a non-enhancing tumor into one that takes up the contrast, likely from radiation effects on the BBB. This may occur within the first 12 months of radiosurgery. This can make the tumor appear to have dedifferentiated into a malignant neoplasm, which would be unlikely in that time frame[17] [Figure 1]. The other reported complications are cystic degeneration. This validates the role of GKRS as an effective adjuvant to surgery in the treatment of LGG. Following the results of the "European Organization for Research and Treatment of Cancer (EORTC)" study evaluating the effects of radiotherapy in LGG patients, standard fractionated radiotherapy can additionally be considered to delay time to progression in high-risk patients.[18]{Figure 1}

Current National Comprehensive Cancer Network (NCCN) guidelines define volume of LGG in pre- and post-operative cases by using fluid-attenuated inversion recovery (FLAIR) and/or T2 signal abnormality on magnetic resonance imaging (MRI) for gross tumor volume (GTV). Clinical target volume (CTV) (GTV plus 1–2 cm margin) should receive 45–54 Gy in 1.8–2.0 Gy fractions. However, NCCN guidelines do not advocate the role of SRS in the management of LGG. Phase I trials using SRS do not support its role as an initial treatment modality (Guidelines available at www.nnc.org).

High-Grade Gliomas

WHO Grade III and IV gliomas pose a significant challenge to neurosurgeons and radiation oncologists alike. Inspite of advances in medical and surgical treatment, the outcome for patients with HGG remains poor. Surgical resection fails to obtain a cure, in spite the most aggressive attempts. Aggressive measures are usually reserved

for cases with good functional status and young age, as these generally pretend relatively good prognosis.[19] There are a number of treatment options for managing WHO grade III and IV glial neoplasms. As the first line of management, maximal cytoreductive microsurgical decompression is pursued. This is usually followed by fractionated conformal radiotherapy with adjuvant chemotherapy consisting of procarbazine, Lomustine, Vincristine (PCV) regime or temozolomide. The extent of surgical resection is highly dependent on tumor location and pre-existing neurological deficits. Some patients with lesions in eloquent areas undergo only biopsy for pathological diagnosis to guide further chemotherapy and radiation treatment.[20] Inspite of aggressive management, the average 2-year survival for glioblastomas remain 27.3% with the median overall survival of 14.6 months.[21]

Efficacy of Gkrs for Hgg

The goal in the management of HGG is not the eradication of the tumor, but rather striking a balance between increasing the length of survival and maintaining an acceptable quality of life (QoL) for the patient. GKRS has been considered as an adjuvant treatment modality, and there has been considerable debate regarding its efficacy. However, it has not been evaluated as a sole treatment for GBM, while most studies evaluating its role as an adjuvant measure.[2]

One of the first studies was that of Souhami and colleagues, reporting on behalf of the Radiation Therapy Oncology Group (RTOG). They conducted a multicenter randomized trial looking at the addition of SRS (including both GKRS and LINAC (linear accelerator)-based radio surgical techniques) to standard external beam radiation therapy (EBRT) for the treatment of GBM.[22] In this trial, SRS was used as part of the initial management of GBM in patients rather than as salvage therapy. The researchers randomly assigned 203 patients with supratentorial GBM to receive either postoperative SRS (prescription dose 15–24 Gy) followed by EBRT and carmustine, or EBRT and carmustine without the preceding SRS. They observed no difference between the two groups of patients with regard to the primary endpoint of survival: the SRS group had a mean survival time of 13.5 months, whereas the control group had a mean survival time of 13.6 months. In spite of no significant difference in survival rates, different timings of GKRS were being evaluated, either at recurrence or with post EBRT boost, or after the same.

Serendipitously, Nwokedi and associates performed a retrospective analysis of patients treated at the University of Maryland during a period of 6 years.[23] Because of a shift in institutional treatment philosophy, the authors changed their practice of administering GKS at the time of tumor recurrence to a scheduled GKS boost within four weeks of the completion of EBRT. This change in practice allowed the authors to compare the two treatment paradigms using overall survival as a measurement of efficacy. They observed a nearly two-fold increase in mean survival time (25 months compared with 13 months) in the groups of patients who received GKRS as a planned boost within four weeks of EBRT. This treatment regimen differs from that of Souhami and coworkers, who administered SRS 1 week prior to the initiation of EBRT.

Most others have used GKRS as an adjuvant measure. Loeffler et al.treated patients with radiosurgery (prescription doses ranging from 10 to20 Gy) 2 to 4 weeks after EBRT, similar to the treatment provided by Nwokedi and colleagues.[23] They also observed a median overall survival rate of 26 months for those patients.[24] Kondziolka et al. have compared their series of patients with GBM, who were treated by GKS with historical control groups. In this series, patients generally received GKRS 5 to 8 months after initial diagnosis (and after other therapies had been completed, including EBRT and chemotherapy), or at the time of recurrence. Patients who received GKRS (mean prescription dose of 15.2 Gy) as part of the initial treatment regimen had an increased median survival of 20 months compared with 11.2 months in the control group. They also reported a median survival of 30 months after GKRS for those patients, who were treated with GKRS at the time of tumor progression.[25] GKRS particularly benefits patients with a Karnofsky performance scale (KPS) Score ranking of at least 90 and those patients who have received adjuvant chemotherapy[26] [Table 2].{Table 2}

However, GKRS being used for glioblastoma treatment is counterintuitive as the former is a form of focused radiation, whereas the latter is the very definition of the diffuse lesion. As demonstrated in the above studies, the treatment when delivered in recurrent or post-surgical cases as in small residual lesion may hold efficacy for treatment.

NCCN defines GTV in HGG in pre- and post-operative MRI imaging using enhanced T1 and FLAIR/T2 images. To account for sub-diagnostic tumor infiltration, the GTV is expanded 1–2 cm (CTV) for grade III and up to 2–2.5 cm (CTV) for grade IV gliomas. However, again SRS does not get a separate mention in NCCN guidelines. It is stressed that the guidelines also suffer a lack of definitive evidence in deciding various treatment modalities with no randomized control trials to define them clearly (Guidelines available at www.nccn.org).

Recurrent Gliomas

Currently, options for treatment for recurrent gliomas include chemotherapy, re-irradiation, surgery, radiosurgery, anti-angiogenic therapy, gene therapy, or palliative care with corticosteroids. The goal of treatment is to avoid the sequelae of iatrogenic neurotoxicity while maintaining a reasonable QoL.[27] Patient's outcome has been shown to be dependent on the KPS, age, and tumor histology. Many patients with recurrent HGG are treated with systemic chemotherapy as a salvage management approach in the form of bevacizumab, temozolomide, irinotecan, marimastat, carmustine, and nitrosoureas.[28] Standard external beam radiation therapy (EBRT) has the advantage of targeting rapidly dividing tumor cells into all areas of the brain while reducing damage to healthy brain tissue. Although the efficacy of standard radiation therapy has been reported in several published series, patients irradiated multiple times are at risk of radiation-related toxicity and necrosis.

RTOG directed a multi-centered randomized phase III trial analyzing the addition of SRS to standard EBRT for the treatment of glioblastoma. In this trial, SRS was used as part of the initial treatment rather than as a salvage therapy. In total, 203 patients with supratentorial glioblastoma were randomly assigned to receive either postoperative SRS followed by EBRT and carmustine, or EBRT and carmustine without SRS. They observed no statistically significant differences between the two groups of patients with regard to the primary endpoint of survival around 13.5 months.[22] There are a number of reviews that have shown encouraging results with respect to survival prolongation in the recurrence setting for specific patients. Elliott et al. irradiated 26 patients with HGG who had previously undergone surgical resection, EBRT, and chemotherapy with GKRS after tumor recurrence. This cohort was then followed up for 12-month actuarial survival for patients with anaplasticastrocytoma, anaplastic mixed oligoastrocytoma, and (GBM) was 80%, 20%, and 37%, respectively. At a median of 4-months after treatment, distant tumor progression was documented in 18 patients (75%). This patient subset showed a high local tumor control rate, with only nine patients (37.5%) found to have a local failure at a median of 5.8 months after treatment.[29] Hsieh et al.[26] in his study of 51 patients with GBM at Northwestern Memorial Hospital treated them with GKRS at the time of tumor progression and reported a median survival of 14.3 months for the entire patient cohort. The 12, 24, and 36-month survival rate of this subset of patients was 68%, 30%, and 24%, respectively. A KPS >90 and the use of adjuvant chemotherapy were important prognosticators of longer periods of survival as in other similar series.[30] Pouratian et al. retrospectively assessed the outcomes of 48 patients with GBM who were given GKRS after standard radiation therapy.[31] Of the 48 patients, 22 were treated as part of their initial treatment regimen and 26 were treated at the time of tumor progression. It was stated that the patients who underwent GKRS at the time of tumor progression had a longer survival ($P < 0.003$) than the patients who underwent GKRS as part of their initial treatment regimen. In addition, on multivariate analysis, they found that patients in recursive partitioning analysis class 3, patients not on steroids at the time of GKRS, and patients with more extensive tumor resections experienced a longer period of survival than the other patients in this cohort.

Thus, GKRS is safe and effective for recurrent HGG. GKRS provides patients with a high local tumor control rate

and median survival after tumor recurrence ranging from 13 to 26 months. Currently, a localized recurrence or limited growth in an eloquent area justifies GKRS followed by chemotherapy. However, clinical research is also needed in analyzing the efficacy and radiation-related toxicities of fractionated GKRS owing to its potential to limit treatment-associated morbidity.

Pediatric Glioma

Diffuse midline glioma introduced in the WHO 2016 classification has subtended a grim shadow on pediatric glioma survival.[32] Histone H3 K27M mutations are found in 80% of diffuse pontine gliomas. These are located in other midline HGGs arising in the thalamus, cerebellum, or spinal cord. These were the first histone mutations to be seen in human cancer. Approximately, 75% of histone H3 mutations occur in H3F3A, encoding the H3.3 isoform, and 20–25% of mutations occur in HIST1H3B or rarely HIST1H3A/C, encoding H3.1. These variants uniformly have a poor prognosis. Furthermore, recurrence may develop in spite the imaging appearance of complete resection, especially in cases of non-pilocytic lesions. However, there have been attempts to treat pediatric gliomas with GKRS.

Grabb et al. (1996) reported a series of 25 cases with a mean age of 8.5 years with pilocytic gliomas as predominant histology.[33] These were treated with a mean peripheral dose of 15.2 Gy (11–20 Gy) with a mean follow-up of 22 months. The investigators showed a 100% survival in pilocytic and grade II gliomas, 80% survival in grade III, and 50% survival in GBM cases. Boethius et al. (2002), similarly, reported a series of 19 cases with a mean age of 10.6 years with pilocytic gliomas being the only histo-pathological diagnosis[34] [Table 3]. These were treated with mean peripheral dose of 11.3 Gy (9-20Gy) with a mean follow-up of 5.9. The investigators showed a 100% survival with 26% adverse radiation effects with one patient requiring re-surgery for radionecrosis, and one case with symptomatic cyst requiring decompression. Weintraub et al. in 2012 studied 24 cases with a mean age of 11 years with mixed subsets of histology. These were treated with a mean peripheral dose of 15 Gy (4–20 Gy) with a mean follow-up of 5.9 years. The investigators showed a 96% survival and 12.5% requiring repeat resection with larger tumor volume predictive of progression.[35]{Table 3}

Although surgical resection remains the bedrock of pediatric glioma treatment, many lesions located in critical areas, such as the brainstem, thalamus, basal ganglia, hypothalamus, or eloquent cortex, cannot be resected without the risk of considerable morbidity and mortality. Moreover, recurrences in the depths of brain or considerable neurological deficit may be incurred in certain cases of pediatric gliomas. Pediatric cases warrant special concerns. Fractionated radiotherapy is generally reserved for children greater than 10 years of age given the significant cognitive adverse effects associated with fractionated radiation in younger patients.[36] Numerous chemotherapeutic regimens are commonly used in younger children to delay the timing of radiotherapy and its connected adverse cognitive effects. GKRS radiosurgery offers benefits over both chemotherapy and fractionated radiotherapy. Apart from it, it remains comfortable being a single day procedure. GKRS seems to be associated with increased rates of progression-free survival and complete tumor response when matched with chemotherapy or fractionated radiotherapy.[36] Although non-quantified, GKRS reduces the risk of secondary malignancy.

Glioma and Metastasis

It is a matter of conjecture that while GKRS is popular for metastasis, it is not very popular for gliomas, although both have a dismal prognosis. In a study analyzing the effect of GKRS on metastasis and gliomas, it was found that in metastatic tumors, rapid tumor regression after radiosurgery was found in 87% of the patients, whereas in gliomas, radiosurgery effectively inhibited tumor growth in selected patients with small, circumscribed, less infiltrative tumors.[37] One of the limiting aspects might also be the treatment size limit of the GKRS for large primary malignant brain tumors, but it is usually not the case in the treatment of metastatic brain tumors.

Cerebral metastases present excellent targets for GKRS because, unlike primary malignant brain tumors, metastatic tumors are usually spherical, small, and well-demarcated from surrounding normal brain tissue. Glioblastomas have highly infiltrative margins, and hence, a focused treatment has not been advocated upfront for these cases. Rather, recurrent or defined margins in LGG may be more amenable to GKRS.[38] With the advancement in imaging and neuronavigation with intraoperative MRI, surgical decompression seems to be a better choice. This is especially true when we consider that decompression offers an immediate reduction in tumor volume in an edematous lesion and thus rapid relief of symptoms.

Imaging-Pre and Post Treatment

When the clinical indications for GKRS have been defined and the patient becomes a suitable candidate for treatment, tumor delineation becomes the sole imaging factor, which determines its favorable response to therapy. It, thus, becomes imperative that the best available imaging modality is utilized for this purpose. MRI is currently the modality of choice for glioma assessment. The standard sequences namely T1-weighted (T1W1), T2-weighted (T2W1), and FLAIR)-weighted are currently employed in tumor segmentation, and the enhancing portion is chosen for GKRS [Figure 2]. However, it is well-known that LGG is typically non-enhancing lesions, and the higher grade ones have spreading margins that extend well beyond their enhancing boundaries [Figure 1]. It, therefore, becomes difficult to precisely define the tumor margins with these sequences[15],[39] [Figure 3]. As a result, most physicians take an extra 1–2 cm margin beyond the visualized enhancing component to include the entire lesion. With advancements in the field of MRI, spectroscopy and perfusion imaging have found a role in delineating this boundary. MR spectroscopy details the biochemical signature of the tumor in the form of elevated choline (Cho) and reduced N-acetyl aspartate (NAA) with often maintained creatinine (Cr) levels. These variations can be derived from changes in the Cho/NAA and Cho/Cr ratios. The precision of lesion localization can be, thus, increased if the structural and spectroscopic parameters are read in unison. Perfusion imaging by dynamic susceptibility contrast imaging or dynamic contrast imaging helps in defining the hypervascularity associated with the tumor. Perfusion parameters may also aid in differentiating tumor recurrence from surgical/radiotherapy induced parenchymal changes, further contributing to increased accuracy of tumor description and delineation. These variables also help in the follow-up of such patients.[39] Although there are no standard guidelines, every patient should be followed with 3D T1 with or without gadolinium administration and T2 images covering the whole lesion every three months for a year followed by at six months for next three years and yearly thereafter for five years.{Figure 2}{Figure 3}

Conclusion

Management of glial tumors primary or recurrent, adult or pediatric patients remains a challenge. We have discussed treatment decisions in terms of GKRS and its emerging role in this subset of highly malignant lesions. Unfortunately, for lesions that cannot be fully or even partially resected without posing a significant risk to the patient, no modality provides control of all tumors. There is increasing evidence that GKRS can provide reasonable control of residual or recurrent gliomas in these patients while preserving neurological status. Poor outcomes are associated with larger tumor volumes at the time of treatment and poorer KPS or older age. For a subset of cases, GKRS offers knife like accuracy and results with minimal morbidity. More randomized controlled trials with better stratification are required to impart more light on this subject.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Figure 1: (a-c) Axial, sagittal, and coronal MRI images of a patient of tectal glioma treated with GKRS. (d-f) follow-up images after 1 year of GKRS showing contrast enhancement in an earlier hypointense lesion suggestive of either dedifferentiation into higher grade lesion or radiation necrosis

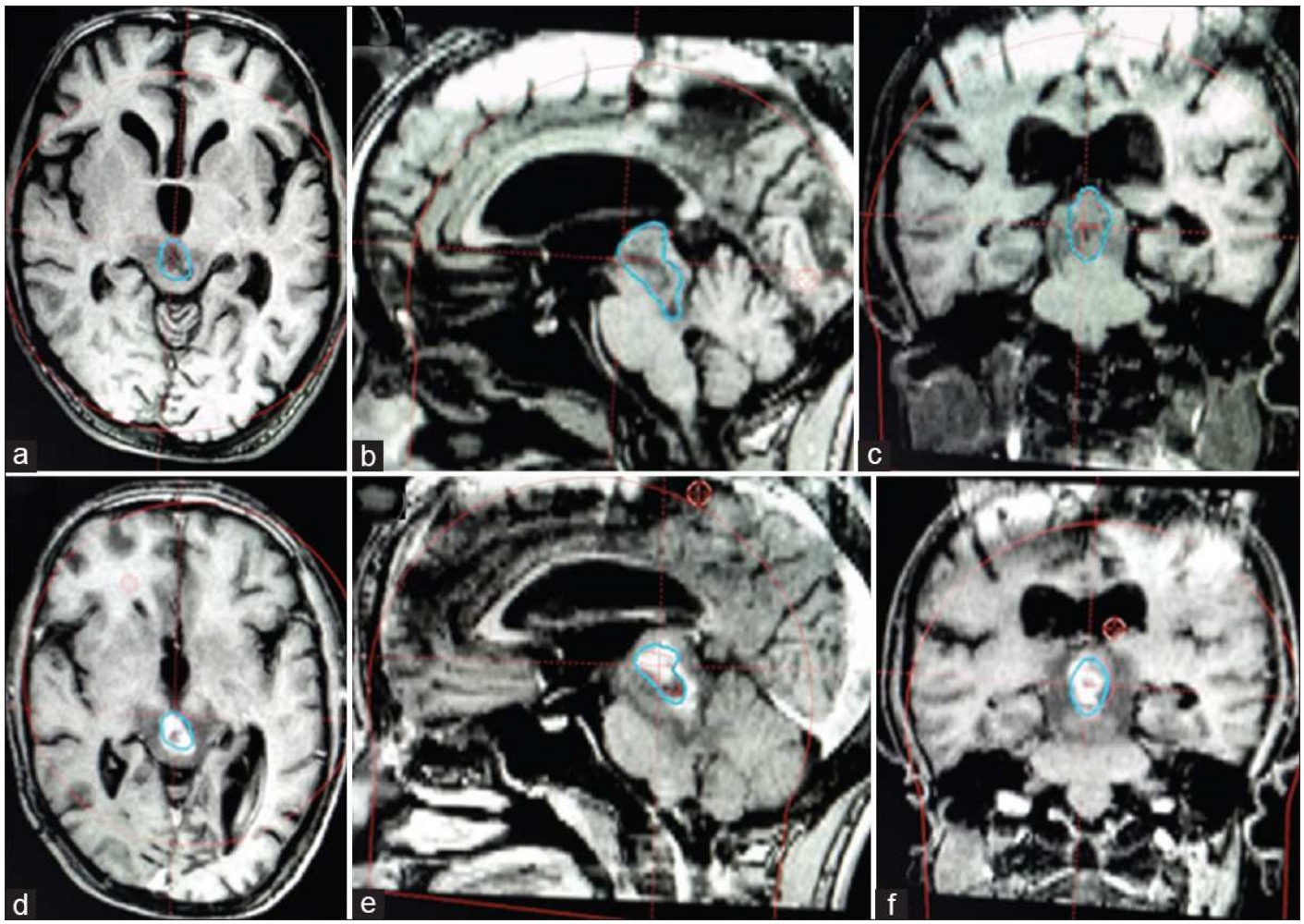

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Figure 2: Gamma knife radiosurgical plan of a recurrent high-grade glioma in left frontal location, treated with 21 Gy marginal dose

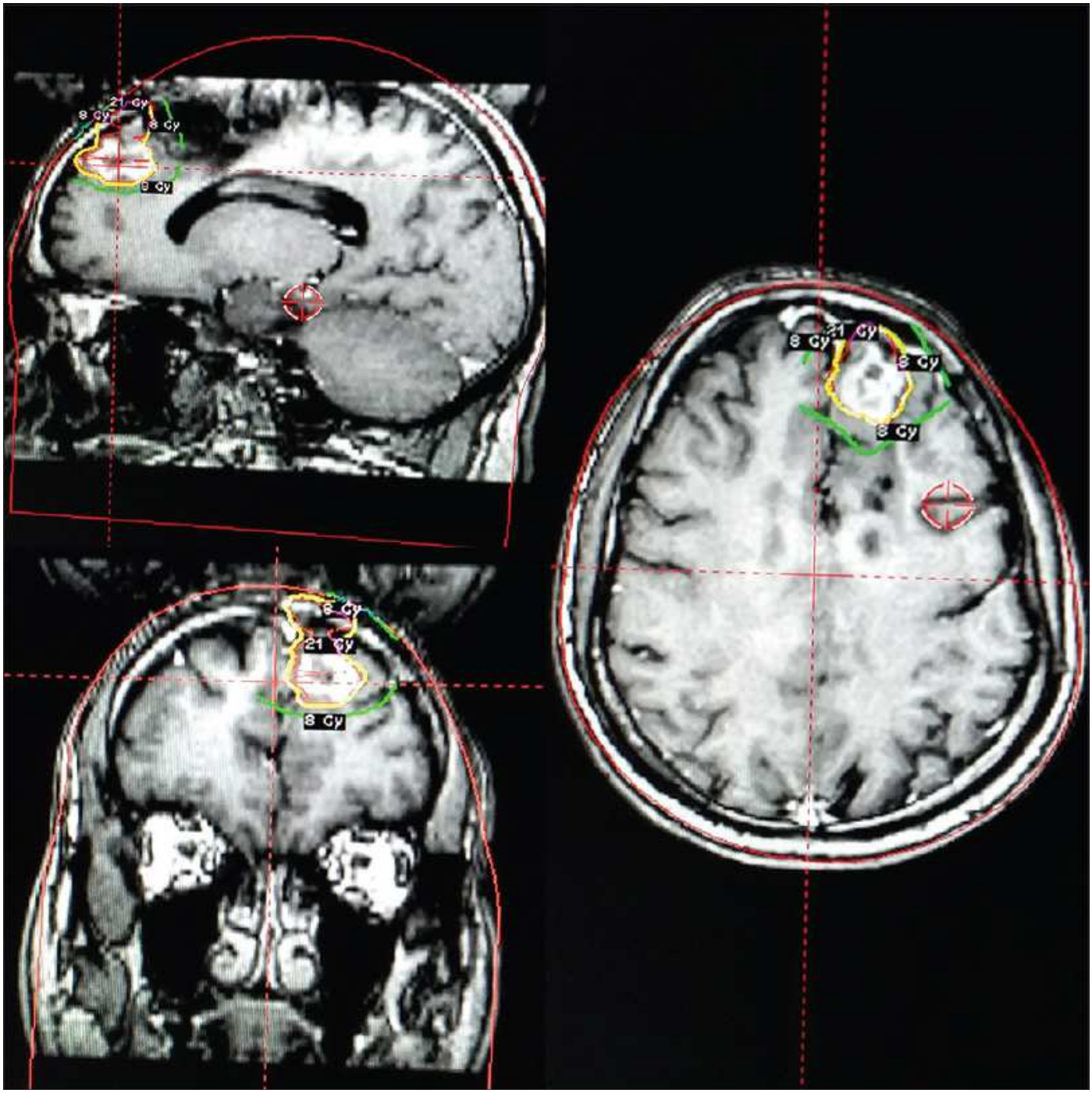

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Figure 3: Axial T2 weighted (a), gadolinium-enhanced T1 weighted (b) images demonstrating the peripherally enhancing centrally necrotic high- grade glioma with peripheral hyperperfusion on dynamic susceptibility contrast imaging (c). Note that the metabolite map showing raised choline on spectroscopy (d) indicates that the solid enhancing zones are the mitotic zones and should always be included in defining the target area for GKRS

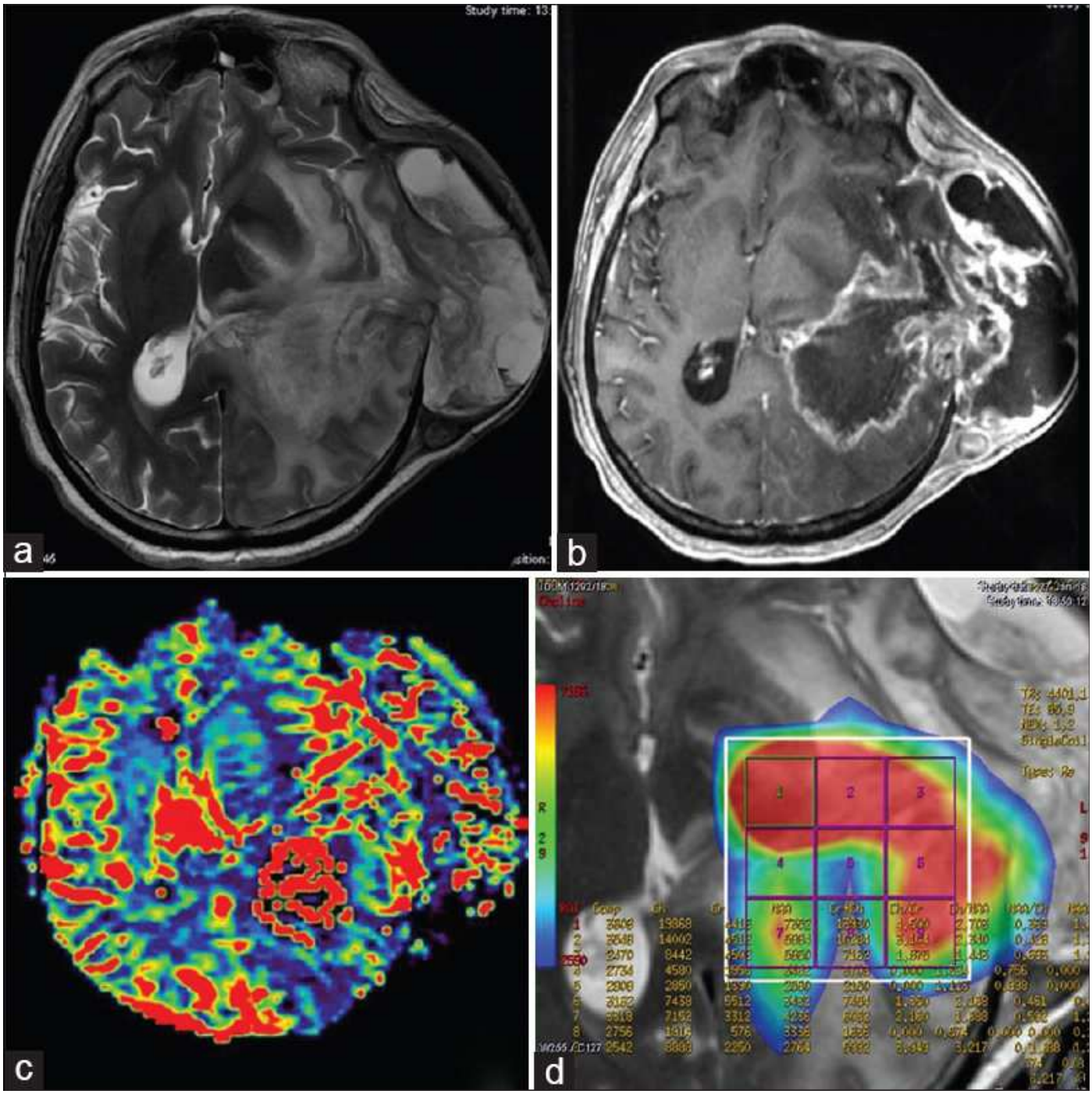

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Table 1: Outcome of gamma knife radiosurgery in cases of pilocytic astrocytoma

Series	Dose (Gray)	Number of patients	Follow-up (months)	Control rate (%)	Outcome
Yen *et al.* (2007)	10-18	20	78	80%	1 died of progress, 1 died of stroke, 2 developed new deficits
Hadjipanayis *et al.* (2002)	15	37	28	76% local control	2 died of progress, 2 developed new deficits, 2 cyst formation
Kano *et al.* (2009)-Pediatric Population	14.5	50	55	70.8% progression-free survival at 5 years	Not available
Kano *et al.* (2009)-Adult Population	13.3	14	36.3	31.5% progression-free survival at 5 years	Cyst formation in 33% cases
Hallemeier *et al.* (2012)	15	18	96	77.8% local control	Cyst formation in 25% cases
Lippitz *et al.*	10	30	146	90%	Cyst formation in 30% cases, 16.7% developed new deficits

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Table 2: Outcome of gamma knife radiosurgery in patients with glioblastoma multiforme (GKRS, Gamma Knife Radiosurgery)

Studies	Mode of treatment	Timing of radiosurgery	Number of cases	Dose (Gray)	Mean survival (months)
Loeffler, *et al.*, 1992	GKRS	Initial	23	12-15	26
Kondziolka, *et al.*, 1997	GKRS	Initial, Recurrence	64	15.5	26
Nwokedi, *et al.*, 2002	GKRS	Initial	64	17.1	25
Souhami, *et al.*, 2004	GKRS and LINAC	Initial	186	15-24	13.5
Combs, *et al.*, 2005	GKRS	Recurrence	32	15	22
Hsieh, *et al.*, 2005	GKRS	Initial, Recurrence	51	12	14.3

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Table 3: Efficacy of gamma knife radiosurgery in pediatric patients of intracranial gliomas

Series	Number of patients	Mean age of patients (Years)	Pathology	Marginal Dose (Gy)	Location of tumor	Outcome (till latest follow-up)
Grabb *et al.* (1996)	25	8.5	Pilocytic-8, Grade II- 5, Grade- III-3, GBM-2, Ependymoma-7	15.2	Not available	100% survival
Boëthius *et al.*, 2002	19	10.6	Pilocytic astrocytoma	11.3	Brainstem-12, Cerebrum- 4, Cerebellum-3	100% tumor control
Weintraub *et al.*, 2012	24	11	Pilocytic astrocytoma-15, Grade II -4, Grade III-1, No pathology (4)	15	Brainstem-13, Cerebrum -6, Cerebellum 5	96% survival