

Research Article

Stereotactic Radiosurgery in the Management of Intractable Seizure Due to Hypothalamic Hamartoma

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Abstract

The occurrence of severe seizure is almost always present in hypothalamic hamartomas (HH) cases and surgery is an option to control the condition. Stereotactic radiosurgery (SRS) is among of alternative treatments. Our objective is to provide current evidence for seizure treatment with SRS in HHs patients. From EuroPMC, PubMed, ScienceDirect and the Cochrane Library, each author carried out literature searches on seizure treatment for HH using SRS between 1971 and 2021 using the following terms: stereotactic radiosurgery, radiosurgery, CyberKnife, Gamma Knife, linear accelerator, radiotherapy and hypothalamic hamartoma. We included any patients with seizure onset less than 18 years of age, regardless of age when SRS was performed. This systematic review included 17 out of 31 studies, three of which were observational studies. The study included 131 individuals, with a median age of onset of 7.4 years old and a male-to-female ratio of 34.3% (n=45). The isodose at the margin was 19 Gy. The median lesion volume at the time of diagnosis was 0.8 mL (0.1 - 48.3 mL). The median follow-up after SRS was 34.3 months (3 - 77 months). Only eight of the 90 HHs had a change in MR and 12 patients, SRS had no effect on the seizure frequency. The authors concluded that SRS is beneficial for the treatment of HH. However, the authors could not deny that current evidence is too early to construct a systematic review and a more prospective study design is required.

Keywords: Hypothalamic Hamartoma; Systematic Review; Stereotactic Radiosurgery

Abbreviations

HH: Hypothalamic Hamartoma; SRS: Stereotactic Radiosurgery; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; JBI: Joanna Briggs Institute's; NOS: Newcastle-Ottawa Scale; CNS: Central Nervous System; M: Male; F: Female; Gy: Gray; SE:

Status Epilepticus; LTG: Lamotrigine; PRI: Primidone; VPA: Valproic Acid; VGB: Vigabatrin; STH: Sulthiame; LEV: Levetiracetam; TPM: Topiramate; OXC: Oxcarbazepine; ESM: Ethosuximide; GBP: Gabapentin; PB: Phenobarbital; GTC: Generalized Tonic Clonic; SPS Simple Partial Seizure; VNS: Vagus Nerve Stimulation; FBM: Felbamate; LINAC: Linear Particle Accelerator; N/A: Not Applicable; CK: Cyber Knife; SBRT: Stereotactic Body Radiation Therapy; AED: Antiepileptic Drugs; AZM: Acetazolamide; Br: Brome; CLB: Clobazam; CPS: Complex Partial Seizures; DPH: Phenytoin; G: Gelastic seizure; GK: Gamma Knife; GM: Secondarily Generalized Seizure

Introduction

Hypothalamic hamartomas are non-neoplastic gray matter malformations made up of hyperplastic neurons of various sizes that are seen in the hypothalamus [1-6]. Epileptic seizures, predominantly gelastic, are the most common signs, especially when they are near to the mammillary bodies [6]. Because seizures are frequently refractory, even with a combination of antiepileptic medications, medical treatment usually fails to provide adequate symptom management. A surgical resection of the hamartoma would be required in these patients. Because of the lesion's deep placement, traditional surgery is technically challenging and carries a high risk of complications, such as diencephalic infarcts and hypothalamic dysfunction [8-19]. As a result, novel stereotactic surgical procedures have been developed in recent years that are less invasive and safer than traditional ones.

SRS is an alternative neurosurgical treatment that may be used to treat refractory symptoms caused by hypothalamic hamartomas [20]. Because of its precision and safety, the GKS approach is currently a well-known and widely applied therapeutic option, particularly for small, deeply seated lesions [8,20]. This procedure avoids open surgery by using stereotactically targeted ionizing radiation to elicit a desired effect in a chosen target with little radiation to the surrounding tissues.

According to current investigations on the neuropathological alterations in tissues after gamma knife treatment, the standard irradiation - mean dosimetry 50% isodose margin of 16 Gy - used to treat resistant hypothalamic hamartomas does not appear to cause necrosis [19]. Non-necrotizing gamma knife radiosurgery doses are thought to be sufficient to reduce cell density in hypothalamic hamartomas, resulting in a reduction in excitation in the neural networks and, as a result, a reduction in seizures.

Arita, et al., published the first example of significant radiological changes after utilizing GKS in treating a HH in 1998 [3]. As a result of a 10 mm hamartoma, this treatment was employed on a 25-year-old patient who had been suffering from refractory epilepsy since he was one year old, showing predominantly gelastic and tonic-clonic convulsions. Seizures were less frequent following the procedure and they eventually stopped 3 months later. A complete elimination of the HH was found in radiological control with MRI 12 months after surgery. This patient has not had any neurological or endocrine complaints and has not had any seizures.

As noted earlier, SRS is an innovative therapeutic choice for HHs that allows great seizure control and a low complication rate. In children, radiosurgery appears to be both safe and successful [3,20]. New technologies that do not require a stereotactic frame may make radiosurgery more accessible to children, providing a completely non-invasive option with few risks. However, no published guidelines comprehensively discuss the use of radiosurgery as an alternative management for hypothalamic hamartoma. Thereby, we aimed to provide current evidence of SRS in HHs patients.

Materials and Methods

From EuroPMC, PubMed, ScienceDirect and the Cochrane Library, each author carried out literature searches on seizure treatment for HH using SRS between 1971 and 2024 using the following terms: stereotactic radiosurgery, radiosurgery, CyberKnife, Gamma Knife, linear accelerator, radiotherapy and hypothalamic hamartoma. According to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), we conducted the systematic review [17,21,30]. We included any patients with seizure onset less than 18 years of age, regardless of age when SRS was performed. We did not make any restrictions on language. Abstract-only articles, opinion, perspective and other non-primary or non-fully published papers were excluded.

The eligibility of 2125 papers found by this query was reviewed by two separate reviewers (JH and MA). The first step was to screen the titles and abstractions. This resulted in a final selection of 14 papers, each of which was evaluated in the full text format. Detailed study examination is presented in Fig. 1. Three independent authors (JH and MA) extracted data and assessed quality using a standardized extraction form that included patients' demographic characteristics (e.g., age of epilepsy onset, age of SRS, duration of seizure or epilepsy, follow-up duration, etc.) from each eligible study. Moreover, we extracted both EEG and radiographic findings from each study. The details of SRS, such as marginal dose, will also be retrieved. If there are any data missing from this systematic review, an email will be sent to the principal investigator of that article. The study endpoint of current study is the subsidence or deterioration of epilepsy for patients with hypothalamic hamartomas undergoing stereotactic radiosurgery.

The initial search and quality rating of each paper were undertaken by two independent reviewers (JH and MA). The Newcastle Ottawa Quality Assessment Scale (NOS) was used to assess case management and longitudinal studies, while the Joanna Briggs Institute's (JBI) essential evaluation checklist for case reports was utilized to examine general consistency of case series and case reports [10].

Any discrepancies between JBI and NOS results were debated until a solution was found. To be considered for this systematic analysis, case reports had to meet the majority of JBI criteria and have a NOS score of at least 7.

Results

Study Selection

The detailed PRISMA study selection diagram is shown in Fig. 1. According to predefined strategy, there were 2125 records obtained from databases. After removing 177 duplicates, 1948 records were obtained to screen. After screened 31 articles for in full text format, 14 articles were excluded because there were no full texts available ($n=3$), publications not in English ($n=2$), studies not in human ($n=4$) and studies that did not report the key outcome of interest of this systematic review ($n=5$).

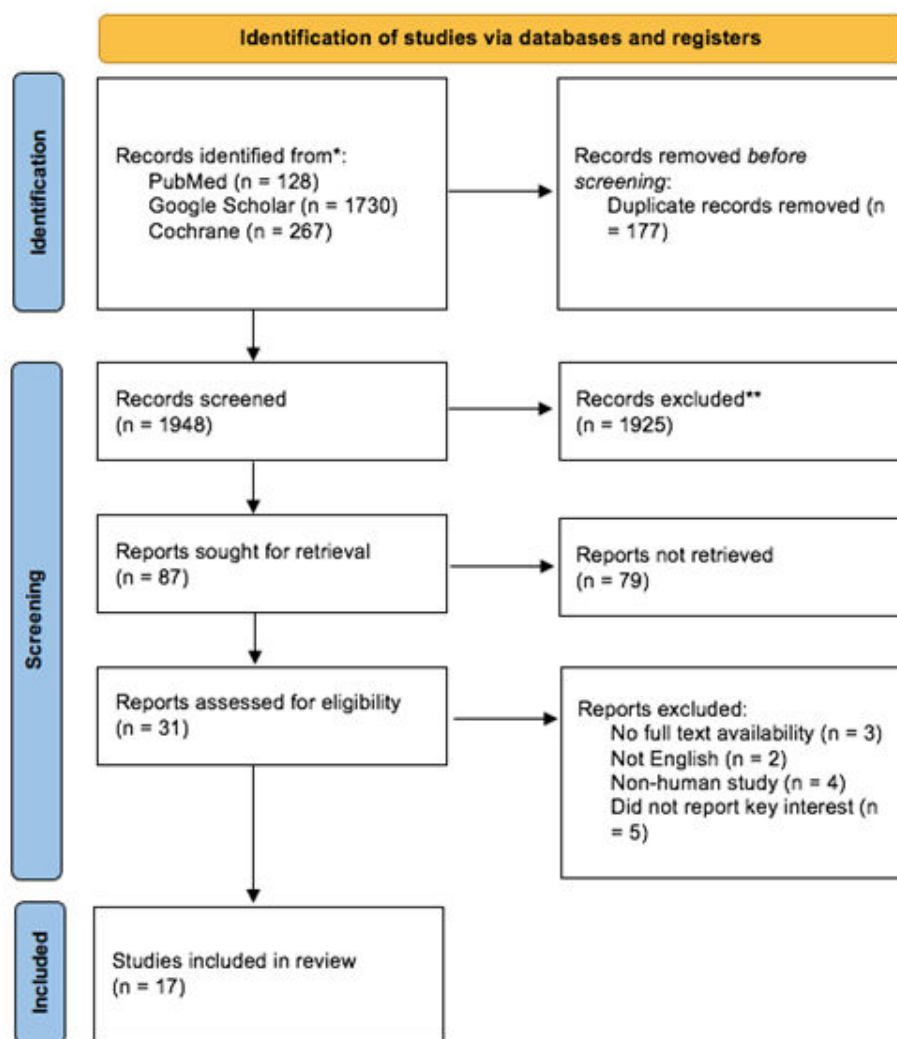


Figure 1: PRISMA study selection diagram.

Study Characteristics

We included 17 studies in this systematic review. The studies consist of 1 prospective study, 2 retrospective cohorts, 8 case reports and 6 case series [1-3,5,9,13,14,16,18-20,23,24-27]. The studies reported the hypothalamic hamartoma patients with Stereotactic

Radiosurgery (SRS), including Gamma Knife Surgery (GK), Cyber Knife (CK), Stereotactic Body Radiation Therapy (SBRT). Most patients in the included studies are treated with Antiepileptic Drugs (AED) before undergoing SRS. 8 studies used Carbamazepine (CBZ) as the most prescribed drugs in the patients, making it as the most drug prescribed in pre-SRS AED medications. Twelve studies shows that patients undergoing resistance in anti-epileptic drugs treatment before undergoing SRS for hypothalamic hamartoma. The baseline characteristics of the included studies and outcomes of the patients are reported in Table 1.

A total of 131 hypothalamic hamartoma patients were included in this study, with 86 patients are male and 45 patients are females. The median age during treatment was 16.6 (1-54) years. The median age of seizure onset was 7.4 (0-19) years. The median marginal dose of radiotherapy to 50% isodose line is 19 Gy (12-60), with median isocenter of 5.5 (1-20). The median lesions volume is 0.8 ml (0.1-48.3), with 8 of 131 showed MR change. The median follow-up of the included studies is 34.3 (3-77) months.

Study Outcomes

Overall, the patients that undergone precocious puberty was obtained in 7 studies that consist of 33 patients, while 13 patients in those 7 studies shown otherwise. 15 studies showed resistance to the AED prior to SRS. In all included studies, after median follow up of 34.4 years after SRS, 65 patients showed decrease of seizure activity after the SRS, 53 patients showed complete cessation of any seizure, while 13 patients showed no benefit at all. In all the included studies, 35 patients have Engel class I after SRS treatment, 27 patients have Engel class II, 18 patients have Engel class III, 14 patients have Engel class IV and 1 patient have Engel class V.

Risk of Publication Bias

Based on JBI assessment, all of the case report studies are considered as “include”, whether in the retrospective cohort studies, all of the included studies have NOS score of 7, therefore all of the retrospective cohort studies are considered good in quality based on NOS. Detailed risk of bias assessment of each included study are presented in Table 2 and Table 3.

First Author, Year	Study Design	Characteristics
Unger, 2000	Case Report	Include
Romanelli, 2018	Case Report	Include
Akai, 2002	Case Report	Include
Mu-ri, 1995	Case Report	Include
Dunoyer, 2002	Case Report	Include
Laiseca, 2016	Case Report	Include
Susheela, 2013	Case Report	Include
Matthieu, 2006	Case Series	Include
Ko, 2006	Case Series	Include
Schulze-Bonhage, 2004	Case Series	Include
Selch, 2005	Case Series	Include
Re'gis, 2000	Case Series	Include
Mathieu, 2010	Case Series	Include

Table 1: Joanna Brings Institute (JBI) Critical Appraisal for Case Reports and Case Series.

Study ID	Study Design	Selection	Comparability	Outcome	Total Score	Result
Re'gis, 2017	Retrospective Cohort	***	*	***	7	Good
Abla, 2010	Retrospective Cohort	****	*	***	8	Good
Re'gis, 2006	Retrospective Cohort	****	*	***	8	Good

Table 2: Newcastle-Ottawa Scale (NOS) for Observational Studies.

Authors & Year	Mean age (years)	Age at seizure onset (year)	Male/precocious puberty/treatment modality	Marginal dose (Gy)	Lesions volume (mL)	Seizure focus (EEG)	Seizure type	Antiepileptic drug	Posttreatment AEDs	Engel class after SRS treatment (I/II/III/IV/V)	Time to improvement (months)/ Follow-up (months)
Arita 1998	25	0.5	1/0/GK	18	NA	Left frontal parietal (1)	G, GTC S	CBZ, VPA, Zonisamide	CBZ and VPA	0/1/0/0/0	3/12
Mathieu 2006	13.5 (5-29)	1.3 (1-2)	2/0/GK	17.5 (16-20)	0.4 (0.2-0.5)	N/A	G, GTC S (4)	Multiple combination AED	Multiple combination AED	0/2/1/1/0	2.3 (2-3)/22 (6-77)
Ko 2006	8.3 (5-12)	0.8 (0.5-1.3)	1/1/GK	17.7 (16-18)	0.3 (0.1-0.5)	bitemporal (1), N/A (2)	G (3)	Multiple combination AED	Reduced dose (1), N/A (1)	1/2/0/0/0	2.3 (0-6)/31 (21-42)
Schulze-Bonhage 2004	17.9 (10-31)	2.7 (0-10)	6/2/SBRT	10.5±3.1	10 (8-11)	N/A	G (7), CPS (7), GM (7),	CBZ (6), DPH (2), LTG (4), PRI (3), VPA (7), LIT (1), VGB (3), STH (1), BR (1), CZB (2), LEV (1), OXC (1), EZM (1), GBP (1), PB (1), VNS (1)	LTG (4), CBZ (1), LEV (3), TPM (1), TPM (1), DPH (1), OXC (1)	2/2/1/1/1	1.4 (0-2)/22.1 (12-36)
Unger 2000	9.5 (6-13)	3 (2-4)	1/1/GK	12	12 (11-13)	Right temporal (1), left hemisphere (1)	G (2), GM (2)	CBZ (1), LTG (1)	CBZ (1), OXC (1)	0/1/1/0/0	10 (8-12)/54
Romaneli 2018	8.5 (8-9)	0 (0-0)	2/0/GK	16	1 (0.9-1.1)	Bitemporal (1)	G (2), GM (2)	Multiple combination AED	N/A	2/0/0/0/0	4.5 (3-6)/30 (18-42)
Re'gis 2017	16.5 (3-50)	1 (0.1-15.2)	27/23/GK	17 (14-25)	4 (0.8-1.6)	N/A	G (48), CPS (48), S (15), GM	N/A	N/A	15/15/12/6/0	N/A/36

							(29)				
Akai 2002	5	3	0/1/GK	25	N/A	N/A	G (1), atonic (1)	CBZ (1), Zonisamide (1)	N/A	N/A	10/16
Abla 2010	15.1 (5.7-29.3)	47.6 (1-476)	8/1/GK	18 (16-20)	0.7 (0.2-3)	N/A	G (8), atonic (1), GTC (3), CPS (6), tonic (1), SPS (1)	Multiple combination AED	Multiple combination AED	6/0/3/1/0	N/A/43.1 (18-81)
Selch 2005	34.7 (11-56)	2 (1-3)	1/0/LINAC	16 (15-18)	0.9 (0.2-2)	Right temporal (1), left temporal (1)	G (3), GTC (1), S (1)	LEV (2), LTG, CBZ (2), DPH (1), PB (1), TPM (2), GBP (1), FBM (1), OXC (1)	TPM (1), OXC (1).	2/1/0/0/0	0.3/12.5 (12-13)
Munari 1995	16	2.5	0/0/LINAC	18	2.34	N/A	G (1), GM (1)	Multiple combination AED	N/A	0/0/0/1/0	NA/15
Dunoyer 2002	9.8 (4-17)	4.2 (0.3-13)	3/0/GK	13.8 (11-15)	1.3 (1-1.5)	Bifrontal (1), right frontal central (1), right central parietal (1), left temporal (1)	G (1), GTC (3)	CBZ (3), PB (2), VPA (2), CZP (1), VGB (1), PRI (1), GBP (1), DPH (1), LTG (1), AZM (1), TPM (1)	OXC (1)	3/0/0/1/0	4.9 (2.5-6)/ 39.3 (26-69)
Re'gis 2000	11.4 (1-25)	1.7 (0.5-3)	4/3/GK	16.9 (12-23.8)	N/A	N/A	G (7), GTC (7)	Multiple combination AED	N/A	N/A	7.3 (0-24)/ 36.6 (12-71)
Laiseca 2016	6	0	1/1/GK	15	1	N/A	G (1), GTC (1)	CBZ (1), Zonisamide (1)	VPA (1)	0/1/0/0/0	3/11
Mathieu 2010	29.8 (12-53)	5.1 (1-8)	5/0/GK	17.2 (14-20)	0.8 (0.3-1.8)	N/A	G (6), CPS (6), GTC	CBZ (5), LTG (2), LEV (3), CZP (3),	CBZ (5), LTG (2), LEV (3), CZP (3),	4/2/0/3/0	N/A/27.6 (6-56)

							(2), GM (2), SPS (1)	OXC (2), DPH (1), VPA (2), CLB (!), TPM (1),	OXC (2), DPH (1), VPA (2), CLB (!), TPM (1),		
Susheela 2013	17	4	1/0/GK	30	48.3	N/A	G	N/A	N/A	N/A	3/3
Regis, 2006	17.2 5 (3- 50)	10.8 mo (0- 228)	1/1/GK	17	6.467	N/A	G,CP S, SPS, GTC	N/A	N/A	N/A	23/51
SE: Status epilepticus; LTG: lamotrigine; PRI: primidone; VPA: valproic acid; VGB: vigabatrin; STH: sulthiame; LEV: levetiracetam; TPM: topiramate; OXC: oxcarbazepine; ESM: ethosuximide; GBP: gabapentin; PB: phenobarbital; GTC: generalized tonic clonic; SPS simple partial seizure; VNS: vagus nerve stimulation; FBM: felbamate; LINAC: Linear particle accelerator; N/A: not applicable; CK: cyber knife; SBRT: Stereotactic body radiation therapy; AED: antiepileptic drugs; AZM: acetazolamide; Br: brome; CLB: clobazam; CPS: complex partial seizures; DPH: phenytoin; G: gelastic seizure; GK: Gamma knife; GM: secondarily generalized seizure.											

Table 3: Descriptive pooled results of studies describing the use of stereotactic radiosurgery in treating intractable seizure for patients with hypothalamic hamartomas.

Discussion

HH is a non-neoplastic gray matter abnormality that occurs between the tuber cinereum and the mammillary bodies in the hypothalamic region.[22] This abnormality has the potential to cause serious behavioral issues as well as cognitive impairment. The idea that the epileptic zone is solely confined to the hamartoma is no longer valid, as studies show that secondary epileptogenesis involves a complex dynamic cortical-subcortical ictal network organization.[15] Nonetheless, the first step in intervention is limited to hamartoma treatment.

Seizures caused by HHs are frequently refractory, even with a combination of antiepileptic medicines, medical treatment usually fails to provide adequate symptom management [4,11]. A surgical resection of the hamartoma would be required in these patients [7]. The lesion's complex anatomical location makes either procedure difficult for the neurosurgeon [12,28]. Despite the fact that endoscopic and interforaminal methods had a superior morbidity profile, endocrinological and cognitive impairment remained a significant disadvantage [29]. As a result, new stereotactic surgical procedures have been developed in recent years that are less invasive and safer than traditional ones. There have been many published articles regarding the use of SRS as a treatment for HHs, but none examine its safety and efficacy. Herewith, we aimed to synthesize a comprehensive systematic review in regard the use of SRS for treating HHs.

Effects on Epileptic Tissue

Regis and colleagues started a treatment using GKS to treat MTLE without space-occupying lesions in 1993. The preliminary findings indicated a high rate of efficacy, no deaths and a very low percentage of long-term neurological impairments (one case of quadrantanopia among seven patients). A marginal dose of greater than 17 Gy is associated with seizure cessation, which is useful information for future GKS operations. However, because their study was retrospective in nature and in accordance with treatment plans, a portion of each lesion near the optic pathways was undercovered, casting doubt on any link between the "marginal" dose and epilepsy treatment efficacy.

Hypothesis for Treating HHs with SRS

SRS is a good way to treat intrahypothalamic lesions that are difficult to completely resect without causing substantial neuro-metabolic sequelae. Small intrahypothalamic or medium-sized sessile intraventricular/inter-peduncular lesions are the most epileptogenic HH. The two largest HH series have a median size of 15 mm and a mean size of 19 mm, respectively. On HH with

similar size, radiosurgical therapy can be safely performed: the steep radiosurgical dose gradients allow for relatively substantial doses to the HH while sparing the nearby important structures. After radiosurgery for HH, no major long-term consequences such as metabolic abnormalities, hemiparesis, cranial nerve deficits, or short-term memory losses have been recorded in the current systematic review. Only 1 patient reported to have a complication of poikilotherm following SRS for HHs. The patient reported by Regis, et al., at their paper published in 2000.

The mechanism of action of SRS, which controls seizures, remains uncertain. The lack of target necrosis revealed by follow-up MRs suggests a neuromodulatory effect caused by gliosis, firing neuron down-regulation and reduced vascular supply.

Drawn from this systematic review, a median of 19 Gy for the margin lesion is found to be effective in treating HHs with the minimum marginal dose of 12 Gy and the maximum of 30 Gy. This seems to be increasing with HHs size. The optimum SRS dose for management of seizures related to HHs cannot be determined from this systematic review. Regis and colleagues hypothesized that there was a dose-response relationship. The median marginal dosage for seizure-free patients was 18.6 Gy, compared to 12 Gy for nonseizure-free patients ($p = 0.029$). All successfully treated patients received a minimum marginal dose of > 17 Gy. Munari and colleagues, on the other hand, found no effect of 18 Gy supplied via LINAC. The incomplete covering of the hamartoma common to patients in that series complicates the anticipated dosage effect described by Regis and associates.

Radiosurgery is not suitable for all HHs. The size of the target is generally known to be the primary restriction of radiosurgery. The very good safety/efficacy ratio of radiosurgery tends to degrade as the volume of the lesion rises for biophysical reasons. As a result, big hamartomas, particularly stage VI hamartomas, are poor candidates for radiosurgery. In a study conducted by Regis and colleagues in 2018, one stage V and one stage VI patient were treated with SRS and both patients entirely failed to respond. On the other hand, current systematic review has shown that median HHs lesion of 0.8 mL seems to be efficacious, despite size of the lesion. This systematic review consists a diverse lesion size from as low as 0.1 mL to as high as 48.3 mL. Our study is consistent with the finding from Susheela in 2013 where the child was treated with a robotic-arm -SRS, which was delivered to a dose of 30 Gy in five fractions over five. Within a week, there was a reduction in the frequency of seizures and by 12 months after the treatment, there had been a complete cessation of seizures. Current study showed that the use of SRS is safe and efficacious regardless of the lesion size. The authors would like to underline that still the marginal dose still need to be prescribed in a higher Gy for larger lesion. There is no doubt that, in order to completely establish this advantage of radiosurgery, a prospective controlled randomized comparative trial with each of the reconstructive and stereotactic procedures would be warranted.

The delayed efficacy of radiosurgery is a one of the limitations of the procedure. The delayed efficacy of GKS may be problematic in patients with very severe epilepsy who are actively deteriorating over time. This study showed that most individuals experienced improvement with a median of 11.5 months. Though seizure does not usually stop immediately following SRS, we noted that seizure stopped within weeks and the latest at 24 months.

Children are especially concerned about potential long-term dangers. To date, only a few examples of patients treated with radiosurgery for different illnesses have been recorded in which a new malignant tumor was identified several years after therapy, near to the initial target of radiosurgery. In several of these cases, a cause-and-effect relationship between radiosurgery and the new tumor looks doubtful, but in others, it is a subject of discussion. According to Lunsford and co-authors, even if all of these cases were acknowledged as being caused by radiosurgery, the risk would still appear to be very low (between 1 case in 10,000 to 100,000 treated patients). In light of the sometimes-disastrous natural history of untreated HH, this risk appears to be acceptable when compared to the likelihood of death after microsurgical excision (1 percent to 2 percent). Parents, on the other hand, should be routinely warned about the possibility of subsequent malignancies following GKS.

This study has a number of significant drawbacks. The occurrence of hypothalamic hamartoma is uncommon, hence this comprehensive study only included 131 individuals. Furthermore, the majority of the paper presented in this study was in the form of a case report. To better understand the impact of HHs size on SRS effectiveness, more research is favourable. The effective minimal dose for HH lesion should be the subject of future research.

Conclusion

For individuals with medically refractory gelastic seizures caused by unresectable hypothalamic hamartomas, SRS is a safe and effective treatment option. The time between therapy and a reduction in seizure frequency is many months with radiosurgery. The extant literature suffers from inherent biases towards this condition and any particular treatment strategy due to its rarity. SRS methods are less intrusive than direct surgery and may enhance hypothalamic hamartoma treatment outcomes. The authors concluded that SRS is beneficial for the treatment of HH. However, the authors could not deny that current evidence is too early to construct a systematic review and a more prospective study design is required.

Conflict of Interests

The authors have no conflict of interest to declare related to this article.

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Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jeremiah H Wijaya and Made AM Inggas. The first draft of the manuscript was written by Jeremiah H Wijaya and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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