Stereotactic radiosurgery as the initial management option for small-volume hypothalamic hamartomas with intractable epilepsy: a 35-year institutional experience and systematic review

*Zhishuo Wei, MSc,1,2 Lena Vodovotz, BS,1,2 Diego D. Luy, MD,1,2 Hansen Deng, MD,2–4 Ajay Niranjan, MD,2–4 and L. Dade Lunsford, MD2–4

1School of Medicine, University of Pittsburgh Medical Center; 2Center for Image-Guided Neurosurgery, University of Pittsburgh Medical Center; and Departments of 3Neurological Surgery and 4Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

OBJECTIVE Young patients with hypothalamic hamartomas (HHs) often present with intractable epilepsy. Currently there are no established management guidelines for HH. The authors retrospectively reviewed their single-institution experience to delineate the role of stereotactic radiosurgery (SRS).

METHODS Seven patients with HHs (4 females; median age 13.7 years, range 2.5–25 years) with no prior resection underwent SRS between 1987 and 2022. The clinical history, epilepsy profile, radiographic findings, and neurological outcomes were characterized. HH topographical types were classified according to the Régis classification. Outcome measures included Engel seizure classification, HH response, and the need for additional surgical interventions.

RESULTS All patients had Engel class IV epilepsy. A Leksell Gamma Knife was used to deliver a median margin dose of 18 Gy (range 16–20 Gy) to a median hamartoma volume of 0.37 cm³ (range 0.20–0.89 cm³). Seizure reduction was confirmed in 6 patients, and 2 patients had regression of their hamartoma. Two patients underwent resection and/or laser interstitial thermal therapy after SRS. At follow-up, 1 patient was seizure free, 4 patients achieved Engel class II, 1 patient had Engel class III, and 1 patient had Engel class IV seizure outcomes.

CONCLUSIONS SRS as the initial management option for HH was associated with a low risk of adverse effects. In this institutional series reviewing small-volume HHs treated with SRS, no adverse radiation effect was detected, and the majority of patients experienced seizure reduction. SRS should be considered as the first-line treatment for seizure control in patients with small-volume HHs.

https://thejns.org/doi/abs/10.3171/2022.9.PEDS22200

KEYWORDS stereotactic radiosurgery; epilepsy; hypothalamic hamartoma; pediatric

HYPOTHALAMIC hamartomas (HHs) are rare entities that consist of mature neurons, glia, and fiber bundles that form during fetal development.1,2 Approximately 95% of HHs arise sporadically, with an estimated incidence of 1 in 100,000 live births.1,3 Patients with HHs often present with gelastic seizures and/or central precocious puberty (CPP) and potentially progress to severe disability in the face of drug-refractory epilepsy.4,5 Seizures with early onset respond poorly to medical therapy and require timely radiosurgical or surgical intervention to prevent severe neuropsychological deficits.6

The current diagnosis of HHs relies on the use of high-resolution MRI. HHs typically are well-demarcated hypointense masses on T1-weighted sequences and are associated with hyperintense signal on T2-weighted sequences.1,7 Resection is often considered the first-line surgical option for large-volume HHs; it is used to improve seizure control while improving neurocognitive and psychiatric function.6,8–10 For small-volume HHs, less invasive first-line interventions are gradually considered for preservation of the patient’s neurological function.9,11 Stereotactic radiosurgery (SRS) is a noninvasive treatment modality...
that has gradually been accepted as the adjuvant therapy for the treatment of HH.\textsuperscript{9,11–13} However, the role of SRS as the primary treatment option for patients with small-volume HHs remains to be defined. The present study describes our 35-year single-institution SRS experience in 7 patients with HHs and emphasizes seizure outcomes.

**Methods**

**Patient Selection**

This study was approved by the University of Pittsburgh's institutional review board. Patients were included if they had epilepsy that remained refractory to adequate antiepileptic drug (AED) therapy, along with demonstration of radiographic imaging features compatible with HHs. Patients were excluded if SRS was used as an adjuvant therapy subsequent to surgical intervention. Pre-SRS baseline information was collected, including age at seizure onset, types of seizures, monthly seizure count, AED usage history, and age at HH diagnosis. A baseline neuropsychology examination was also performed.

In total we identified 7 patients with HHs (4 female, 3 male) who underwent SRS without prior surgical intervention during a 35-year interval from 1987 to 2022. We reviewed individual chart records to evaluate the subsequent medical and surgical management strategies applied in these patients, concentrating on the long-term epilepsy outcomes. The following variables were included: age; sex; HH treatment volume; duration of seizure symptoms; classification of seizures (i.e., gelastic, dacrystic, absence, tonic, simple partial, complex partial, generalized tonic-clonic; age at HH diagnosis; endocrinological status; and behavioral and developmental abnormalities. The median age at seizure onset was 3.2 years (range 1–10 years), with a median interval from seizure onset to HH diagnosis of 4 years (range 0.5–21.8 years). The median age at HH diagnosis was 12 years (range 2.5–25 years). At the time of SRS, all patients had drug-refractory epilepsy characterized as Engel class IV.

**Radiosurgery Protocol**

Informed consent for the procedure was obtained from the patient or their caregiver. For patients younger than 12 years of age, general anesthesia was given. For older patients, local anesthesia (mixture of lidocaine 1% and bupivacaine 0.25%) was given along with conscious sedation (fentanyl given intravenously). A Leksell stereotactic headframe was then applied to each patient, and a contrast agent (gadopentetate dimeglumine 469 mg/ml, 0.2 ml/kg) was used to obtain high-resolution axial plane T1-weighted brain MRI (1.5-mm slice) for HH localization. Axial fast spin echo T2-weighted images (3-mm slice) were also obtained to delineate the relationship of the HH to adjacent critical intracranial structures, including the hypothalamus, the pituitary gland, and the optic apparatus. SRS plans were made with the goal of complete HH coverage, with maximal 20-Gy coverage. Each SRS plan was reviewed and approved by a team consisting of a neurosurgeon, radiation oncologist, and medical physicist. Adjacent critical neurological structures including the brainstem and the hypothalamus were visualized through contouring by the radiation oncologists (Fig. 1). Beam channel blocking techniques were applied as needed to improve the radiation dose falloff in the adjacent hypothalamic, pituitary, and optic nerve structures. The radiation dose fallofoffs on the optic apparatus and brainstem were kept below 8 Gy and 10 Gy, respectively. Various models of the Leksell Gamma Knife (models U, B, 4C, and

---

**TABLE 1. Preoperative characteristics of patients with HHs**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age at Sz Onset (yrs)</th>
<th>Age at HH Dx (yrs)</th>
<th>Sz Onset to HH Dx (yrs)</th>
<th>Sz Types</th>
<th>Sz Frequency</th>
<th>Endocrinopathy</th>
<th>Neuropsych Sxs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>3.2</td>
<td>25</td>
<td>21.8</td>
<td>Gelastic; complex partial; tonic-clonic</td>
<td>5–10 monthly</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>2</td>
<td>2.5</td>
<td>0.5</td>
<td>Gelastic; absence; tonic-clonic</td>
<td>5–10 daily</td>
<td>No</td>
<td>Aggressive behavior; developmental delay</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>Absence; tonic-clonic; atonic</td>
<td>&gt;100 daily</td>
<td>No</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>Gelastic; tonic-clonic</td>
<td>Daily</td>
<td>No</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>Gelastic</td>
<td>6–10 daily</td>
<td>Central hypothyroidism</td>
<td>Aggressive behavior; developmental delay</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>1</td>
<td>12</td>
<td>11</td>
<td>Absence; complex partial; tonic-clonic</td>
<td>Daily</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>1.2</td>
<td>5</td>
<td>4</td>
<td>Absence; complex partial</td>
<td>Daily</td>
<td>No</td>
<td>Attention deficit; aggressive behavior; developmental delay; autism</td>
</tr>
</tbody>
</table>

Dx = diagnosis; NA = not available; Neuropsych Sxs = neuropsychiatric symptoms; Sz = seizure.

At the time of SRS, all patients had drug-refractory epilepsy characterized as Engel class IV.
Perfexion; AB Elekta) were used for the single-session radiation delivery. After radiation delivery, the stereotactic headframe was removed and the patient was discharged on the same day.

**HH Topography Classification**

HH topography and the lesion’s relation to hypothalamus provides valuable information in facilitating the neurosurgeon’s decision-making and predicting the patient’s clinical outcome. Several protocols have been developed in describing HH neuroradiological topography. Delalande and Fohlen categorize HHs by the plane of insertion of the tumor on the hypothalamus, with recommendations of the most appropriate surgical approach (i.e., pterional disconnection, endoscopic approach, or a combination of the two). The HH classification system proposed by Régis et al. focuses on the anatomical location of HHs in relation to the hypothalamus and third ventricle. Whereas the Delalande system clearly delineates surgical approaches suited to different types of HH, given that the goal of SRS for HH is complete tumor coverage rather than disconnection, and that radiation of nearby structures is a major cause of morbidity in SRS, the Régis system was chosen to describe both HH and the surrounding topology in the context of stereotactic surgical planning.

**Literature Inclusion Criteria**

A comprehensive and systematic search was conducted in the National Library of Medicine PubMed database for all human studies published on HH treated with SRS. Given the rarity of this disease, many cases of HH in the literature have largely been case reports. Here, we decided to focus on comparable studies and have included large institutional case series that used SRS as the dominant treatment modality. We have excluded studies focused on resection and/or laser interstitial thermal therapy (LITT) along with case reports or small case series with fewer than 5 patients. In accordance with PRISMA guidelines, these case series and their results (SRS technique, number of cases treated, age at diagnosis, age at SRS treatment, median margin dose, HH volume, seizure semiology, psychiatric comorbidity, endocrine abnormality, seizure outcomes, and total follow-up) have been included to assist in delineating the role of SRS in the treatment of HH. To limit potential bias, all authors approved of methods for literature review and results.

**Results**

Clinical and MRI follow-up was performed at 3-month intervals for the 1st year after SRS and then yearly during the ensuing 3–5 years. The HH response to SRS was monitored according to the Response Assessment in Neuro-Oncology (RANO) criteria. Clinical evaluation by the patient’s epileptologist and characterization of seizure type and frequency were assessed. The Engel classification of seizure control (class I, free of disabling seizures; class
II, rare disabling seizures; class III, worthwhile improvement; class IV, no significant improvement) was used to measure the effect of SRS on seizure frequency. The HH volume at the last follow-up MRI session was compared to the pre-SRS volume to determine the overall volumetric change. The need for additional adjuvant therapy after SRS, including delayed resection (n = 2) or LITT (n = 1), was evaluated during long-term follow-up. Pre-SRS and post-SRS neurocognitive function assessments were available in 5 patients.

### Treatment Characteristics

The median interval from HH imaging–based diagnosis to SRS was 7 months (range 5–36 months) and the median patient age at SRS was 13.7 years (range 5.1–29.9 years). A median margin dose of 18 Gy (range 16–20 Gy) was prescribed for the HH margin, with delivery at 50% isodose for all patients. The median maximum dose was 36 Gy (range 32–40 Gy). The median HH volume was 0.37 cm$^3$ (range 0.20–0.89 cm$^3$). No patient had a biopsy or a history of resection prior to SRS. A single patient had undergone placement of a vagal nerve stimulator before SRS, with minimal reduction in seizure frequency (Table 2).

#### HH Response

The median follow-up was 57 months (range 21–104 months; Table 3). At the last follow-up, 2 patients had more than 20% reduction in volume compared to pre-SRS. Five patients had imaging volume changes of ± 20%. HH classification was performed according to the Régis grading system.$^{16,17}$ Type I HHs are attached to the floor of the third ventricle or suspended from the floor by a peduncle and are associated with CPP or are asymptomatic. Type II HHs are enveloped by the hypothalamus and eventually distort the third ventricle and are associated with seizures. Type III HHs have combined features of type I and II HHs. Neuroimaging showed that 2 patients had type I HH, 2 patients had type II, and 3 patients had type III.

---

**TABLE 2. Summary of SRS treatments**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Interval From HH Dx to SRS (mos)</th>
<th>Age at SRS (yrs)</th>
<th>HH Vol (cm$^3$)</th>
<th>Régis Grade</th>
<th>Margin Dose (Gy)</th>
<th>Maximal Dose (Gy)</th>
<th>Prescription Isodose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>29.9</td>
<td>0.51</td>
<td>III</td>
<td>18</td>
<td>36</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>6</td>
<td>0.22</td>
<td>I</td>
<td>18</td>
<td>36</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>14.1</td>
<td>0.20</td>
<td>I</td>
<td>20</td>
<td>40</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>21</td>
<td>0.37</td>
<td>II</td>
<td>16</td>
<td>32</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>13.7</td>
<td>0.20</td>
<td>II</td>
<td>19</td>
<td>38</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>5.3</td>
<td>0.69</td>
<td>III</td>
<td>18</td>
<td>36</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>5.1</td>
<td>0.55</td>
<td>III</td>
<td>16</td>
<td>32</td>
<td>50%</td>
</tr>
</tbody>
</table>

**TABLE 3. Follow-up and outcomes after SRS**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>FU Post-SRS (mos)</th>
<th>Transient Increase in Szs</th>
<th>Engel Classification at Latest FU</th>
<th>Sz Types</th>
<th>Sz Outcome</th>
<th>HH Vol Regression$^*$</th>
<th>Neuropsych Sxs Change</th>
<th>Additional Tx</th>
<th>AEDs at Latest FU</th>
<th>Alive at Latest FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>No</td>
<td>II</td>
<td>Gelastic, complex partial, tonic-clonic</td>
<td>Improved</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>LTG 150 mg BID; CBZ 900 mg BID</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>No</td>
<td>II</td>
<td>Gelastic, absence, tonic</td>
<td>Improved</td>
<td>No</td>
<td>Stable</td>
<td>Resection</td>
<td>CBZ 400 mg BID; ZNS 100 BID</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>No</td>
<td>IV</td>
<td>Absence, tonic-clonic, atonic</td>
<td>Stable</td>
<td>No</td>
<td>Stable</td>
<td>No</td>
<td>LEV 500 mg TID; OXC 2400 mg; LTG 100 mg BID</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>No</td>
<td>III</td>
<td>Complex partial, tonic-clonic</td>
<td>Improved</td>
<td>Yes</td>
<td>Improved</td>
<td>Resection; LITT</td>
<td>VPA 750 mg BID; ZNS 300 mg BID; LAC 200 mg BID</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>104</td>
<td>No</td>
<td>II</td>
<td>Gelastic, absence</td>
<td>Improved</td>
<td>No</td>
<td>Stable</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Yes†</td>
<td>II</td>
<td>Gelastic, complex partial, tonic-clonic</td>
<td>Improved</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>VPA 450 mg BID</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>No</td>
<td>I</td>
<td>Absence, complex partial</td>
<td>Seizure free</td>
<td>No</td>
<td>Stable</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BID = twice a day; CBZ = carbamazepine; FU = follow-up; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; Tx = treatment; VPA = valproic acid; ZNS = zonisamide.

$^*$ Yes = HH regression defined as > 20% decrease in original HH volume; no = change in HH volume defined as ± 20% of original HH volume.

† Seizures initially worsened but reduced in frequency 1.5 years after SRS.
Epilepsy Outcomes

Six patients had a significant reduction in their overall seizure frequency. From their original Engel class IV seizure frequency, 1 patient was seizure free, 4 patients achieved Engel class II, and 1 achieved Engel class III after SRS. One child remained Engel class IV with no significant improvement in seizure frequency. A single patient experienced a transient increase in seizure frequency, followed by overall decrease in seizure frequency 1.5 years after SRS. Two patients underwent post-SRS resection and/or LITT due to HH enlargement. Both patients had improved seizure outcomes at the latest clinical follow-up. A single patient died 11 years after SRS from an unknown cause (Fig. 2, Table 3).

Behavioral and Endocrine Outcomes

Pre-SRS cognitive symptoms included mild developmental delay (5 patients), aggressive and hyperactive behaviors (3 patients), and autism (1 patient). Six patients exhibited no major change in behavioral patterns. One patient exhibited behavioral improvement (Table 3). No patients exhibited endocrinological dysfunction after SRS.

Discussion

Despite their relatively benign histology, the location and effects of HH lead to significant negative quality-of-life implications for both the patient and their caregivers. HH-associated epilepsy is heterogeneous in seizure characteristics, with the majority of patients (73%) experiencing daily gelastic seizures. Their epilepsy is frequently drug resistant and associated with progressive psychiatric and neuropsychological morbidity. Neuropsychiatric disorders include aggressive behavior, anxiety, depression, attention deficit hyperactivity disorder, and obsessive-compulsive disorder. For large-volume symptomatic HHS, both resection and, more recently, LITT have been considered as the best initial surgical options. The role of SRS as the initial surgical strategy for seizure reduction remains to be clarified. This is the first study evaluating the seizure outcomes in patients with HHSs undergoing SRS as the initial management.

By location, HHSs in the posterior hypothalamus and mammillary bodies are associated with gelastic seizures, and patients with these lesions near the anterior hypothalamus or tuber cinereum have CPP. Gelastic seizures typically emerge in infancy and some may resolve at approximately the age of 10 years. Other seizure types include tonic-clonic, complex partial, atonic, and absence seizures. In children exhibiting CPP, symptoms include pubarche, menarche, and tall stature. If left untreated, the symptoms can progress to hirsutism, increased musculoskeletal growth, and enlarged genitalia.

Clinical presentation has been noted to vary between pediatric and adult patients with HHSs. Mullatti et al. have noted that children with HH-associated epilepsy have more severe seizures, with gelastic seizures as the predominant form of manifestation. In another case series of exclusively adult patients, Mullatti noted that later onset of epilepsy is associated with milder epilepsy syndrome, less severe learning difficulties and behavior problems, and better occupational and social status. In the present series, 5 of 7 patients were diagnosed with HHSs at the age of 12 or younger, with gelastic seizure being the predominant form of seizure, and all patients presented with Engel class IV seizure. Of the 4 pediatric patients with HHSs
in whom a baseline neuropsychological examination was obtained, aggressive behavior and attention deficits were noted (cases 2, 5, and 7). In comparison, for the patient in case 4 in whom HH was diagnosed at the age of 20 years, despite the presence of gelastic seizure and the epilepsy severity classified as Engel class IV, aggressive behavior and attention deficits were absent.

Small-volume HHs can be easily missed on radiographic imaging. In our patients the median HH size was 0.37 cm³. If standard MRI studies are acquired as slices of 2-mm thickness with an interslice gap of 5 mm, an HH with a diameter of 5 mm or less may not be identified. The difficulty of detecting small-volume HHs as well as their rarity delays identification of seizure etiology, leading to progressive tumor enlargement and irreversible cognitive deficits. In our study, the median age at seizure onset was 3.2 years and the clinical diagnosis of HHs was delayed after the age of 12 years.

HH topography and the relation to the hypothalamus provides valuable information in facilitating the neurosurgeon’s decision-making and predicting the patient’s clinical outcome. Hypointense on T1, iso- to hyperintense on T2, and minimally contrast enhancing on MRI, HHs can extend to nearby structures including the third ventricle, the lateral wall of the hypothalamus, and the tuber cinereum. Surgical removal of HHs requires particular knowledge and understanding of the anatomical structures adjacent to the lesion, including hypothalamic nuclei, mammillary bodies, optic chiasm, and brainstem, as well as the pituitary gland and stalk. Injury to these structures may lead to additional neurological deficits. Different from the surgical focus of disconnection, radiosurgery treatments of HH focus on full coverage with small-volume HHs. Hamdi et al. noted that the clinical presentation of epileptic HH is significantly affected by topography patterns, with lateral extension within the hypothalamus associated with severe epilepsy, higher seizure frequency, and more severe psychiatric comorbidity. The authors concluded that post-SRS the seizure outcome was not affected by the invaded hypothalamic areas and that full HH coverage should be the goal during the radiosurgery planning procedures. In the current study, patients with HHs of Régis type I–III were included. Similarly, no correlation between post-SRS seizure outcome and invasion of the hypothalamic area was noted.

Previous studies also showed that 37.9%–65.4% of HHs cannot be completely resected. In a case series of 29 patients with HHs, Wang et al. reported that gross-total resection could not be achieved in 38.5% of the patients, and that most patients underwent reoperation. For these reasons, SRS has emerged as an excellent treatment option in patients with residual HHs and epilepsy. Especially in patients with small and medium-sized HHs, SRS provides excellent symptom control. Similarly, in a case series in which Gamma Knife SRS was applied in 48 patients with a median HH volume of 0.398 cm³ with a median margin dose of 17 Gy, Hamdi et al. noted that 68.8% of patients achieved Engel class II or better seizure outcome after SRS. The authors advocate for Gamma Knife SRS treatment for smaller-volume HHs (Régis type I–II). In our study, the HH treatment volume (median HH volume 0.37 cm³) was comparable to that in the earlier literature, with all patients presenting with Régis type I–III. After SRS, 70% of the patients achieved seizure outcome improvements.

Table 4 summarizes the prior literature related to the use of SRS for HH. The favorable outcome of seizure improvements was reported in studies in which SRS was used for treatment of small-volume HHs. In the largest study, Régis et al. described 57 patients with HHs and severe epilepsy who underwent SRS. In their series, a median margin dose of 17 Gy was prescribed to a median HH volume of 0.4 cm³. The median age at SRS was 16.5 years. After SRS, global psychiatric disability resolved in 28% of patients and improved in 56% of patients. Drees et al. compared the seizure outcomes for patients with HHs who underwent SRS versus resection. Only 4 patients underwent SRS (median margin dose of 18 Gy, median HH volume of 0.54 cm³), but these patients had a similar rate of seizure improvement (50%) compared to resection.

Several prognostic factors have been noted in predicting the seizure outcome. As Drees et al. have pointed out, the absence of mental retardation was a significant favorable prognostic factor in predicting seizure outcome for patients with HHs who underwent either resection or Gamma Knife SRS. Similarly, Hamdi et al. reported that Gamma Knife SRS significantly improved cognitive functions in patients with HHs, with significantly better cognitive improvement observed in post-SRS seizure-free patients compared to the non–seizure-free patients, indicating the correlation between the post-SRS seizure and cognitive outcome.

In addition to seizure outcomes, psychiatric comorbidities remain another important challenge in the treatment of HH. A favorable cognitive improvement outcome has been reported in the past studies. Hamdi et al. reported that significant cognitive improvements, including working memory index and processing speed index, were noted in patients with HHs 3 years post-SRS, with no decline observed in intellectual ability.

Presently, HH treatment includes microsurgical resection, SRS, and/or LITT. Multimodality management should be advocated to maximize seizure reduction, and HH anatomical features are an important factor in facilitating the neurosurgeon’s clinical decision-making. Patients with type I HHs are the best candidates for SRS given that the lesions are both small and deeply embedded in the hypothalamus, making invasive microsurgical resection challenging. Although type II HHs may be surgically resected via the endoscopic and transcallosal interfornical approach, treatment with SRS minimizes the risks of worsening short-term memory, endocrinological abnormalities, and thalamic or thalamocapsular infarcts. SRS is also preferable in type III HHs. Given their proximity to mammillary bodies and the fornix, type IV HHs may be resected via a pterional approach or orbitozygomatic craniotomy. However, if they are small, SRS provides added safety. Despite the efficacy and safety of treatment with SRS, a notable disadvantage is its delayed action. LITT provides another stereotactic modality to treat HH. Although LITT has been noted to provide a minimally invasive method to destroy pathological tissue, it has exhibited...
TABLE 4. Review of previous institutional case series or multicenter studies

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Technique</th>
<th>No. of Pts</th>
<th>Age at Dx in Yrs (range)</th>
<th>Age at SRS in Yrs (range)</th>
<th>Median Margin Dose in Gy (range)</th>
<th>HH Vol in cm³ (range)</th>
<th>Sz Types (no.)</th>
<th>Psychiatric Comorbidity (no.)</th>
<th>Endocrine Abnormality (no.)</th>
<th>Sz Outcomes (no.)</th>
<th>Total FU in Mos (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamdi et al., 2021¹²</td>
<td>SRS</td>
<td>39</td>
<td>3 ± 4 (0–18)</td>
<td>17 (4–50)</td>
<td>17 (14–20)</td>
<td>0.48 ± 0.53 (0.07–2.71)</td>
<td>NR</td>
<td>Anxiety, depression, aggression, mood disorders, OCDS, phobia, avoidant, or antisocial (24)</td>
<td>CPP (14)</td>
<td>Engel I (17), Engel II (13), Engel III (4), Engel IV (5)</td>
<td>71 (36–133)</td>
</tr>
<tr>
<td>Hamdi et al., 2021³³</td>
<td>SRS</td>
<td>48</td>
<td>1 (0.1–15.2)</td>
<td>16.5 (3–50)</td>
<td>17 (14–25)</td>
<td>0.40 ± 0.43 (0.08–1.60)</td>
<td>Gelastic (NR), non-gelastic focal-onset impaired awareness (NR)</td>
<td>Psychiatric comorbidity (38), hyperactivity (17), aggression (34)</td>
<td>CPP (23)</td>
<td>Engel I (19), Engel II (14), Engel III (8), Engel IV (7)</td>
<td>71 (36–135)</td>
</tr>
<tr>
<td>Wagner et al., 2014³⁸</td>
<td>¹²⁵I-seed</td>
<td>26</td>
<td>4 ± 3.5 (0–12)</td>
<td>26.7 ± 12.2 (8–53)</td>
<td>60 (10.6 cGy/hr)</td>
<td>1.4 ± 1.4 (NR)</td>
<td>NR</td>
<td>Gelastic (NR), non-gelastic focal-onset impaired awareness (NR)</td>
<td>NR</td>
<td>¹²⁵I-seed Engel I (19), Engel II (14), Engel III (8), Engel IV (7)</td>
<td>12.9 ± 5.9 (3–36)</td>
</tr>
<tr>
<td>Kerrigan et al., 2013³⁹</td>
<td>SRS</td>
<td>10</td>
<td>NR</td>
<td>13.7 (3–29.9)</td>
<td>16 (6–29.1)</td>
<td>1.60 (0.08–7.26)</td>
<td>Gelastic (9)</td>
<td>Psychiatric comorbidity (38), hyperactivity (17), aggression (34)</td>
<td>CPP (7)</td>
<td>Engel I (19), Engel II (14), Engel III (8), Engel IV (7)</td>
<td>71 (36–133)</td>
</tr>
<tr>
<td>Drees et al., 2012¹⁸</td>
<td>SRS</td>
<td>40 (4 SRS)</td>
<td>17 (0–55)</td>
<td>27 (18–55)</td>
<td>18 (16–20)</td>
<td>0.54 (0.09–11.19)</td>
<td>Gelastic (36), complex partial (29), generalized (3), myoclonic (1), drop (5)</td>
<td>NR</td>
<td>CPP (16)</td>
<td>Engel I (10), Engel III (17), Engel IV (8)</td>
<td>70 (12–94)</td>
</tr>
<tr>
<td>Quiske et al., 2007⁴⁰</td>
<td>¹²⁵I-seed</td>
<td>14</td>
<td>4.2 ± 3.9 (NR)</td>
<td>25.4 ± 10.5 (15–43)</td>
<td>60 (NR)</td>
<td>0.971 ± 0.879 (NR)</td>
<td>Gelastic (14), simple partial (NR), complex partial (NR), secondarily generalized (NR)</td>
<td>NR</td>
<td>CPP (7)</td>
<td>&gt;50% reduction (5), no improvement (9)</td>
<td>3</td>
</tr>
<tr>
<td>Régis et al., 2004¹⁵</td>
<td>SRS</td>
<td>30</td>
<td>0.5 (0–19)</td>
<td>16 (3–40)</td>
<td>17 (14–20)</td>
<td>NR</td>
<td>G elastic (30), complex partial (30), generalized (18)</td>
<td>Inhibition (6), aggression (15), hyperkinetic (8), hallucinations (3)</td>
<td>CPP (20)</td>
<td>Improved frequency (18), resolved partial complex seizures (7)</td>
<td>28 (12–71)</td>
</tr>
<tr>
<td>Régis et al., 2017¹⁹</td>
<td>SRS</td>
<td>57</td>
<td>1 (0–15.2)</td>
<td>16.5 (3–50)</td>
<td>17 (14–25)</td>
<td>0.40 (0.08–1.60)</td>
<td>Gelastic (57), focal (47), secondarily generalized (16), tonic (4)</td>
<td>Aggression (34), hyperkinetic (17), autistic features (8), OCD (1), suicidal anxiety (1), paranoia (1), bulimia (2), depression (2), hallucinations (2)</td>
<td>CPP (23)</td>
<td>Engel I (15), Engel II (15), Engel III (12), Engel IV (6)</td>
<td>71 (36–153)</td>
</tr>
<tr>
<td>Régis et al., 2000¹⁶</td>
<td>SRS</td>
<td>10</td>
<td>2 (0.5–27)</td>
<td>13.5 (1–32)</td>
<td>15.25 (12–20)</td>
<td>0.65 (0.134–2.67)</td>
<td>Gelastic (10), complex partial (10), generalized (10)</td>
<td>NR</td>
<td>CPP (3)</td>
<td>Seizure-free (4), partially improved (4), rare nocturnal seizures (1), rare partial seizures (1)</td>
<td>28 (12–71)</td>
</tr>
<tr>
<td>Tuleasca et al., 2022⁴²</td>
<td>SRS</td>
<td>24</td>
<td>3 ± 3 (1–20)</td>
<td>9 (5.9–50)</td>
<td>17 (14–25)</td>
<td>0.269 (0.096–1.207)</td>
<td>Gelastic (24), complex partial (24), generalized (16)</td>
<td>NR</td>
<td>CPP (14)</td>
<td>Engel I (8), Engel II (7), Engel III (3), Engel IV (6)</td>
<td>NA</td>
</tr>
<tr>
<td>Present study</td>
<td>SRS</td>
<td>7</td>
<td>12 (2.5–25)</td>
<td>13.7 (5.1–29.9)</td>
<td>18 (16–20)</td>
<td>0.37 (0.20–0.89)</td>
<td>Gelastic (5), complex partial (3), generalized (4), absence (4)</td>
<td>Aggression (3), autistic features (1)</td>
<td>Central hypothyroidism (1)</td>
<td>Engel II (4), Engel III (1), Engel IV (2)</td>
<td>34 (9–104)</td>
</tr>
</tbody>
</table>

NR = not reported; OCD = obsessive-compulsive disorder; pts = patients.

With the exception of the patients in Tuleasca et al. (in whom no pre-SRS AEDs were reported), all patients in all of the other studies received pre-SRS AEDs. Unless otherwise indicated, values are expressed as either the median (range) or the mean ± SD (range).
limitations in the treatment of HH, and long-term seizure outcomes have yet to be explored. Risks of direct lesioning with LITT can include injury to small thalamoperforate arteries en passage, considerations that are taken into account as part of preoperative planning.\textsuperscript{17,36}

In our experience, radiographic HH volume changes after SRS were not associated with changes in clinical symptomology. The benefit of SRS is probably related to the inhibition of ictal activity from epileptogenic foci, and less so by the reduction in the HH volume.\textsuperscript{11,18,37} SRS was able to preserve endocrinological function, without development of new adverse neurocognitive or behavioral changes.

Conclusions

In this small series of patients accumulated over almost 35 years, we found that SRS for small-volume HHS resulted in improvement in epilepsy outcomes in most patients while maintaining neurocognitive function. Although the procedure is minimally invasive and low risk, the role of SRS in larger-volume HHS, especially in comparison to other surgical options, remains to be explored.

References

34. Li CD, Luo SQ, Tang J, Jia G, Ma ZY, Zhang YQ. Classifica-

Disclosures
Dr. Lunsford has direct stock ownership in AB Elekta; is a consultant for Teledoc, Inc.; and is chair of the data and safety monitoring board at Insightec.

Author Contributions
Conception and design: Deng, Niranjan, Lunsford. Acquisition of data: Deng, Wei, Vodovotz, Luy. Analysis and interpretation of data: Deng, Wei. Drafting the article: Wei, Vodovotz. Critically revising the article: Deng, Wei, Niranjan, Lunsford. Reviewed submitted version of manuscript: Deng, Wei, Niranjan, Lunsford. Approved the final version of the manuscript on behalf of all authors: Deng. Statistical analysis: Wei. Study supervision: Deng, Niranjan, Lunsford.

Correspondence
Hansen Deng: University of Pittsburgh Medical Center, Pittsburgh, PA. dengh3@upmc.edu.