Hypothalamic hamartoma (HH) is an intrinsic epileptogenic lesion causing gelastic seizures (GS). HHs also provoke not only other types of seizures but also behavioral and cognitive problems. Because these seizures are medically intractable, surgical treatment is undertaken with the intention of cure. However, with the surgical approach, it is difficult to achieve sufficient treatment of deep-seated HHs surrounded by critical structures. Many reports on surgical treatment have mentioned the high rate of complications.

We have reported the high efficacy and minimal invasiveness of stereotactic radiofrequency thermocoagulation (SRT) in early series. Although the average size of HHs is reported to be around 14 to 19 mm, there are rare cases of giant HHs with a maximum diameter greater than 30 mm. There are several case reports of surgically treated giant HHs because their sizes and complex shapes can present a challenge to surgery. We have dealt with many giant HHs and have performed SRT for such patients with the same strategy as for HHs of the usual size. We have come to believe that SRT is applicable for any size or shape of HH because it is a stereotactically secured procedure with minimal invasiveness.

In the present study, the clinical data of our giant HH cases were retrospectively reviewed to validate the efficacy and safety of SRT.

OBJECTIVE The authors undertook this study to validate the feasibility and safety of stereotactic radiofrequency thermocoagulation (SRT) for the surgical treatment of giant hypothalamic hamartoma (HH).

METHODS Of the 109 patients who underwent SRT for hypothalamic hamartoma (HH) at the authors’ institution between 1997 and 2013, 16 patients (9 female, 7 male) had giant HHs (maximum diameter ≥ 30 mm). The clinical records of these 16 patients were retrospectively reviewed.

RESULTS The patients’ age at first SRT ranged from 1 to 22 years (median 5 years). The maximum diameter of their HHs was 30–80 mm (mean 38.5 mm). Eleven HHs had bilateral attachments to the hypothalamus. All patients had gelastic seizures (GS), and 12 had types of seizures other than GS. Some of these patients also had mental retardation (n = 10, 62.5%), behavioral disorders (n = 8, 50.0%), and precocious puberty (n = 11, 68.8%). A total of 22 SRT procedures were performed; 5 patients underwent repeat SRT procedures. There was no mortality or permanent morbidity. After 17 of the 22 procedures, the patients experienced transient complications, including high fever (n = 7), hyperphagia (n = 3), hyponatremia (n = 6), disturbance of consciousness (n = 1), cyst enlargement (n = 1), and epidural hematoma (n = 1). Thirteen patients (81.3%) achieved freedom from GS after the final SRT procedure during a follow-up period ranging from 6 to 60 months (mean 23 months). Twelve patients had non-gelastic seizures in addition to GS, and 7 (58.3%) of these 12 patients experienced freedom from their non-gelastic seizures.

CONCLUSIONS SRT provided minimal invasiveness and excellent seizure outcomes even in patients with giant HHs. Repeat SRT is safe for residual GS. SRT is a feasible single surgical strategy for HH regardless of the tumor’s size or shape.

KEY WORDS gelastic seizure; giant hypothalamic hamartoma; stereotactic radiofrequency thermocoagulation; surgical treatment; stereotactic radiosurgery
Methods

Patient Profiles

Of 109 consecutive patients with HHs who underwent SRT at Nishi-Niigata Chuo National Hospital between 1997 and 2013, 16 patients (9 female, 7 male) had giant HHs (maximum diameter ≥ 30 mm). The clinical records of these 16 cases were analyzed in this study. Preoperative evaluation included clinical history, seizure semiology, neurological examination, neuropsychological tests, endocrinological examination, electroencephalography (EEG), video-EEG, CT, MRI, and interictal and ictal single-photon emission computed tomography (SPECT) with 99mTc-ethylcysteinate dimer.

MRI and Ictal SPECT

For SRT, lesions were classified on the bases of coronal MR images into intrahypothalamic type, mixed hypothalamic type, and parahypothalamic type according to Kameyama’s classification.19 The attachment to the hypothalamus was also categorized as unilateral or bilateral attachment based on the continuity with the hypothalamus. Ictal SPECT was analyzed using subtraction ictal SPECT coregistered to MRI (SISCOM). Details of MRI and SISCOM have been described elsewhere.18

Surgical Strategy

The basic SRT procedure has been described previously.19 The most important point of the SRT strategy is to achieve sufficient coagulation of the interface of the hamartoma with the hypothalamus. The trajectory of the coagulation probe is set to pass through the interface using 3D image planning software (Leksell SurgiPlan, Elekta). The location of the probe is confirmed by intraoperative fluoroscopy in each trajectory. Deviation within 1 mm is considered acceptable. If the probe deviates by more than 1 mm, it is reinserted with some adjustment. Then, a coagulation lesion with a 5-mm diameter is created along a trajectory to disconnect the attachment of the hamartoma. For all giant hamartomas, multiple lesions were configured through multiple unilateral trajectories (Fig. 1). Because giant hamartomas have not only a large and complex interface, but also bilateral attachments, the trajectory must be carefully planned. For HHs with bilateral attachments, the approach side is determined by the major attachment to the hypothalamus, the results of SISCOM, and seizure semiology. Some giant HH cases show an area of increased blood flow on SISCOM at the dominant attachment. This finding is considered to indicate the site of ictogenesis.

Although multi-staged SRT procedures were intention-
ally planned for giant HHs to allow for creation of separate trajectories for treating the bilateral attachments, we developed a method involving a unilateral approach to the ipsilateral attachment and a trans–third ventricular approach to the contralateral attachment in a single-stage procedure and have been using this method since 2013 (Fig. 2). Repeat SRT procedures were performed for patients who had residual or recurrent GS, basing our decision on postoperative MRI performed at least 3 months after SRT. Because postoperative MRI performed immediately after SRT shows edema, swelling, and hemorrhage within the hamartoma, such a study is not appropriate for making decisions about residual hamartoma. The approach side was determined in the same way as for the first SRT, as described above. Repeat SRT was not performed for treatment of residual non-gelastic seizures.

Follow-Up Study

The patients were routinely followed up at 3 months, 1 year, 2 years, 3 years, and 5 years after SRT. Routine follow-up included EEG, MRI, neuropsychological tests, and endocrinological examination. Patients with residual GS also underwent video-EEG for confirmation of the seizures. Our main concern was whether seizures remained at the follow-up visits, and if so, which types of seizures they were. Seizure outcomes were classified by family members and the comprehensive epilepsy team as complete seizure freedom or lack of complete seizure freedom and evaluated in patients with at least 1 year of follow-up. Some patients with apparent residual GS underwent repeat SRT within 1 year after the previous SRT. For patients who underwent multi-staged SRT procedures, the follow-up period was counted from the final SRT.

Results

Clinical Characteristics

The patients’ median age at first SRT was 5 years (range 1–22 years). The mean maximum HH diameter was 38.5 mm (range 30–80 mm). Overall, 15 patients showed mixed-type HHs, and 1 patient had a parahypothalamic-type HH. Eleven HHs had bilateral attachments to the hypothalamus. All patients had GS. The median age at onset of GS was 0 years (range 0–4 years), and the median age at onset of other seizure types was 1.75 years (range 0–11 years). Non-gelastic seizure types included complex partial seizures, tonic seizures, atonic seizures, and generalized tonic-clonic seizures. Ten patients had only GS; 6 patients had non-gelastic seizures in addition to GS. Mental retardation, behavioral disorders, and precocious puberty were also present in 10 (62.5%), 8 (50.0%), and 11 (68.8%) of the patients, respectively. Pallister-Hall syndrome was confirmed in 3 patients. Eight patients underwent previous interventions, including direct open resection (in 5 cases), endoscopic resection (in 1), SRT at another institute (in 1), and radiosurgery (in 6). Three of these patients had undergone multiple procedures before being treated with SRT at our institution. A summary of the patients’ demographic and clinical characteristics is provided in Table 1.

FIG. 2. Case 15. T1-weighted MR images illustrating SRT performed via the trans–third ventricular approach. The preoperative coronal MR image (A) shows a giant, mixed-type, bilaterally attached HH with a large cyst. The trajectory of the coagulation probe is planned to make coagulated lesions at the interface, as for basic SRT (B). Thereafter, the trajectory targeted to the contralateral attachment is configured through the third ventricle (C). The trajectories are combined to cover the whole bilateral interface (E, axial; F, sagittal; G, coronal). The postoperative coronal MR image obtained 1 year after SRT (D) shows that the coagulated lesion was made not only at the operated side, but also at the contralateral attachment (G). This patient remained seizure-free at the 1-year follow-up evaluation. For details of what the circles and dotted lines indicate, see the Fig. 1 legend.
SRT Procedures

A total of 22 SRT procedures were performed in the 16 patients included in this study (Table 2). Five patients underwent multistaged SRT. In the first SRT procedure, a mean of 5.9 tracks (range 3–10 tracks) and 16.6 lesions (range 6–36 lesions) were necessary. In the following SRT procedures, a mean of 4.6 tracks (range 3–6 tracks) and 17.9 coagulated lesions (range 6–36 lesions) were required. In the following discussion, cases 1–6, 8–14, and 16 are shown in Figs. 1 and 2. Postoperative MRI showed that the coagulations were made not in the whole hamartoma, but were focused at the border between the hamartoma and the hypothalamus.

Seizure Outcomes

The mean duration of follow-up was 24.1 months (range 12–60 months). Thirteen patients (81.3%) achieved complete freedom from GS after the final SRT. Repeat SRT is planned for 2 of the 3 patients with residual GS in the near future; the remaining patient is under observation, but a decision has not yet been made regarding repeat SRT in this case. Of the 12 patients who had non-gelastic seizures, 7 (58.3%) experienced freedom from these seizure types. Residual non-gelastic seizures included tonic seizures (in 4 patients) and generalized tonic-clonic seizures (in 2). One patient had both tonic and generalized tonic-clonic seizures. Overall seizure freedom was achieved in 10 cases (62.5%). Seven patients were able to reduce their antiepileptic drug (AED) therapy, and 2 of them were able to discontinue AED treatment entirely.

Discussion

A total of 22 SRT procedures were performed in 16 patients with giant HHs, and overall seizure freedom was achieved in 62.5% of the cases. In 13 patients (81.3%), GS ceased completely after treatment. After 17 of the 22 SRT procedures, several complications, including Horner’s syn-
## TABLE 2. SRT procedures, complications, and seizure outcome

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Ap = approach side; CD = consciousness disturbance; Cys = cyst enlargement; EpiH, epidural hematoma; FU = follow-up; HF = high fever; HS = Horner's syndrome; HyP = hyperphagia; Le = number of coagulation lesions; Na = hyponatremia; perm = permanent complications; procs = procedures; Tr = number of trajectories; trans = transient complications.

*After final SRT.

†Trans–third ventricle approach.
drome, high fever, hyperphagia, hyponatremia, consciousness disturbance, cyst enlargement, and epidural hematoma, were encountered. However, all of these complications were transient, and they did not result in long-term impairment of the patients’ quality of life.

HH is an intrinsic epileptogenic lesion causing medically intractable epilepsy, characterized by unusual seizures, i.e., GS. HHs also cause various types of seizure other than GS as well as cognitive impairment and behavioral disorders. These problems are thought to be the effect of HH as secondary epileptogenesis or epileptic encephalopathy. Cognitive and behavioral problems are surgically remediable, so this pathophysiology is considered treatable epileptic encephalopathy. Direct open surgery, including a transcallosal, pterional, or orbitofrontal approach; endoscopic surgery; and radiosurgery have all been performed for resection or disconnection of the HHs.

Surgical procedures for HH have been able to achieve seizure freedom or significant seizure reduction in approximately 50%–60% of cases, although they were frequently associated with some mortality or morbidity.

### Table: Preoperative and Postoperative MRI Images

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<th>SRT (coronal)</th>
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**Fig. 3.** Cases 1–4. Preoperative MR images (upper rows), representative images from the SRT procedures (middle rows), and final postoperative MR images (lower rows). In each set of preoperative or postoperative MR images, the axial image is on the left and the coronal image on the right. Two images are shown for both axial and coronal views in Case 4 in order to demonstrate the complex shape of this patient’s extremely large HH. Final postoperative MRI studies were performed at least 3 months after the final SRT. For details of what the circles and dotted lines indicate, see the Fig. 1 legend.
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cause HHs are surrounded by numerous critical structures, such as major brain structures (hypothalamus, pituitary gland, mammillary body, fornix, cerebral peduncle), cranial nerves (optic tracts and oculomotor nerves), and major vessels, approaches to the HHs through the basal cistern or the ventricle carry a high risk of injury to these structures. Therefore, every surgical approach has inevitable risks of hypothalamic symptoms, hypopituitarism, memory problems, and stroke.26,28 Furthermore, the border between a hamartoma and normal hypothalamus is quite difficult to distinguish visually, making it difficult to achieve sufficient disconnection by a transventricular or endoscopic approach. Because sufficient disconnection of a hamartoma from the hypothalamus is essential for seizure freedom, incomplete disconnection may result in residual seizures. Gamma Knife surgery (GKS) has been used to treat HHs and has achieved passable seizure outcomes equivalent to surgical approaches. Radiosurgery has the great advantage of increased safety compared with resection or disconnection surgery, but it has limitations, because large or giant HHs are not appropriate for GKS.1,24,35 Moreover, GKS has some disadvantages in immediate results, and some patients also experienced acute seizure exacerbation.34

Safety and Efficacy of SRT

The minimal invasiveness and efficacy of SRT for pa-

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FIG. 4. Cases 5, 6, and 8–10. Preoperative MR images (upper rows), representative images from the SRT procedures (middle rows), and final postoperative MR images (lower rows). In each set of preoperative or postoperative MR images, the axial image is on the left and the coronal image is on the right.
SRT for giant hypothalamic hamartoma

Patients with intractable epilepsy due to HH has been described in early reports. SRT is based on stereotactic technique, which guarantees accuracy and less invasiveness. Our SRT technique using 3D image planning software provides accurate targeting within 1-mm deviation confirmed by intraoperative fluoroscopy on each insertion of the trajectories. The diameter of the coagulated lesion is 5 mm, which is equal to that of the sphere planned in SurgiPlan (Figs. 1 and 2). We check that the diameter of the coagulated lesion created by each coagulation probe is 5 mm by test-heating egg albumin before every SRT procedure. Therefore, the interface of the hamartoma can be disconnected according to the presurgical plan with great accuracy. The ultimate goal of the treatment of epilepsy due to HH is disconnection of the hamartoma from the hypothalamus, because HH is intrinsically epileptogenetic, and direct epileptic propagation to the hypothalamus and thalamus generates GS. Although coagulations were not performed in the whole hamartoma, excellent seizure outcomes, better than with previously reported treatments, were achieved.

When patients are treated with SRT, the interface of the hamartoma can be disrupted without any damage to the critical structures outside the hamartoma. In SRT, the coagulation probe penetrates white matter and a small part of the basal ganglia, but such limited damage does not

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![Image](image7.png)

**Fig. 5.** Cases 11–14 and 16. Preoperative MR images (upper rows), representative images from the SRT procedures (middle rows), and final postoperative MR images (lower rows). In each set of preoperative or postoperative MR images, the axial image is on the left and the coronal image is on the right.
cause any neurological deficit, even when multiple tracks are used. The only risks are hemorrhage and edema of surrounding and penetrated tissues. There were no massive hematomas during the period of this study, only minimal bleeding across the coagulation probe tracks or within the coagulated lesion. Edema does occur around the coagulated lesion, and an effect on hypothalamic function can be expected. Most of our patients experienced signs of symptoms of hypothalamic dysfunction, such as high fever, hyperphagia, hyponatremia, Horner’s syndrome, and memory disturbance. However, in all but 1 case, they were transient and improved quickly, usually within 2 weeks. One patient had a prolonged disturbance of consciousness, probably because of bilateral hypothalamic dysfunction due to bilateral coagulation in the second SRT, but even this patient had recovered fully by 3 months after SRT.

SRT has the advantage of having an immediate effect on seizure cessation if effective. This feature is superior to that of GKS, which has similar safety. For some patients it is sheer pleasure to have a seizure-free life immediately after treatment. The minimally invasive procedure of SRT can achieve this with minimal and transient adverse effects.

Giant HH

Comparatively large series have reported that the average size of HHs ranges from 14 to 19 mm.2,8,13,16 Eleven cases of giant HHs, defined as over 30 mm, could be identified in the literature.2,8,13,16,23,25,27,32,33 Some reports included giant HHs, although precise information was unavailable.11,28 We accumulated 16 cases in our own consecutive series. To the best of our knowledge, the present study is the first single specialized report of such a large number of surgically treated cases of giant HHs.

The past articles made negative comments about the surgical treatment of giant HHs.1,2 In most reports, the seizure outcomes were unfavorable, and surgical treatment of giant HHs was accompanied with a high incidence of complications. Because a giant HH has complex attachments and adheres to surrounding structures, surgical procedures other than SRT are characterized by difficulty in disconnecting or resecting the HH from the hypothalamus. Delalande and Fohlen classified giant HHs as Type IV in their classification system and mentioned that no specific surgical procedures can be recommended.7 GKS has also been described as unsuitable for giant HHs.24,34 Some authors have mentioned that there was no single strategy for HHs, or they recommended combination therapy regardless of the size or the shape of the HH.1,2,6,10 They surgical procedures may have some limitations in the treatment of HHs.

SRT can coagulate the border of the hamartoma accurately, independent of size, shape, and location. In our series of giant HHs treated with SRT, a favorable outcome—freedom from GS—was achieved in 13 of 16 cases. Additionally, there were no permanent complications in any of the SRT procedures. SRT can be safely repeated for residual areas of connection between the HH and the hypothalamus; a total of 7 repeat SRT procedures were performed in 5 patients, and, furthermore, one of these patients underwent a total of 4 SRT procedures. Even in patients who underwent repeat SRT, there were no permanent complications, and the rate of transient complications did not increase. One patient who underwent a second SRT procedure for the treatment of residual bilateral attachments had a relatively prolonged but transient disturbance of consciousness. We hypothesized that severe edema occurred in hypothalamus bilaterally, causing the impaired consciousness. Giant HHs sometimes require aggressive treatment for complete disconnection, so that special care in the accuracy of targeting is needed. We guarantee accuracy by performing rigorous preplanning with 3D image planning software and by confirming the location of the inserted coagulation probe. Although early reports on SRT mentioned that it should be used for patients with small or medium-sized HHs,6,22,38 we consider that sophisticated SRT is the best single treatment for HHs, without any limitation of size, shape, or location.

Conclusions

We have reported on a series of 16 cases of giant HHs treated with SRT. Favorable seizure outcome was achieved without any permanent complications. We conclude that SRT is the best surgical treatment for HHs, even giant HHs.

Acknowledgments

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References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Shirozu, Kameyama. Acquisition of data: Shirozu, Masuda, Ito, Sonoda. Analysis and interpretation of data: Shirozu. Drafting the article: Shirozu. Critically revising the article: Shirozu. Reviewed submitted version of manuscript: Shirozu, Kameyama. Approved the final version of the manuscript on behalf of all authors: Shirozu. Study supervision: Kameyama.

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