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## Surgical treatment of hypothalamic hamartomas

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## Abstract

Hypothalamic hamartomas are aberrant masses, composed of abnormally distributed neurons and glia. Along endocrine and cognitive symptoms, they may cause epileptic seizures, including the specific gelastic and dacrystic seizures. Surgery is the treatment of drug resistant hamartoma epilepsy, with associated positive results on endocrine, psychiatric and cognitive symptoms. Recently, alternatives to open microsurgical treatment have been proposed. We review these techniques and compare their efficacy and safety.

Open resection or disconnection of the hamartoma, either through pterional, transcallosal or transventricular approach, leads to good epileptological control but its high complication rate, up to 30%, limits its indications. The purely cisternal peduncular forms remain the only indication of open, pterional, approach, while other strategies have been developed to overcome the neurological, endocrine, behavioral or cognitive complications.

Laser and radiofrequency thermo-coagulation based disconnection through robot-guided stereo-endoscopy has been proposed as an alternative to open microsurgical resection and stereotactic destruction. The goal is to allow safe and complete disconnection of a possibly complex attachment zone, through a single intraparenchymal trajectory which allows multiple laser or radiofrequency probe trajectory inside the ventricle. The efficacy was high, with 78% of favorable outcome, and the overall complication rate was 8%. It was especially effective in patients with isolated gelastic seizures and pure intraventricular hamartomas.

Stereotactic radiosurgery has proved as efficacious and safer than open microsurgery, with around 60% of seizure control and a very low complication rate. Multiple stereotactic thermo-coagulation showed very interesting results with 71% of seizure freedom and 2% of permanent complications. Stereotactic laser interstitial thermotherapy (LiTT) seems as effective as open microsurgery (from 76% to 81% of seizure freedom) but causes up to 20% of permanent complications. This technique has however been highly improved by targeting only the epileptogenic onset zone in the hamartoma, as shown on preoperative functional MRI, leading to an improvement of epilepsy control by 45% (92% of seizure freedom) with no postoperative morbidity.

All these results suggest that the impact of the surgical procedure does not depend on purely technical matters (laser vs radiofrequency thermo-coagulation or stereotactic vs robot-guided stereo-endoscopy) but relies on the understanding of the epileptic network, including inside the

hamartoma, the aim being to plan an effective disconnection or lesion of the epileptogenic part while sparing the adjacent functional structures.

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## Introduction

Hypothalamic hamartomas (from ἀμαρτία, sin) are rare heterotopic masses resulting from an aberrant development of normal tissue that arise from the ventral hypothalamus<sup>40</sup>. They are composed of abnormally distributed but cytologically normal neurons and glia, including fibrillary astrocytes and oligodendrocytes<sup>19,46</sup>. Hypothalamic hamartomas can be isolated, associated with other brain lesions, or be part of malformative disorders, for instance the Pallister-Hall syndrome, a genetic disease caused by GLI3 frameshift mutations<sup>38</sup>. These developmental malformations can be diagnosed incidentally<sup>16</sup> or during investigation of neurological, psychiatric or endocrine disturbances<sup>46</sup> according to their anatomical location. When the lesion is in contact with the infundibulum or with the tuber cinereum, endocrine signs are frequently present, especially precocious puberty<sup>17</sup>. Epilepsy and behavioral or cognitive disorders are associated with hypothalamic hamartomas connected with the mamillary bodies<sup>55,76</sup>. Epilepsy usually starts during the first year of life with the classical gelastic seizures<sup>46</sup> (from γέλως, laugh) or less frequently dacrytic (from δάκρυ, tear) seizures<sup>12</sup>. These very specific seizures have first been reported during the late XIX<sup>th</sup> century by Armand Trousseau<sup>75</sup> as an “irrepressible pulsion to laugh”. The term “gelastic” was introduced in 1957<sup>21</sup>, and description of gelastic attacks defined in 1971 as “characterized by repeated short-lasting seizures with initial emotionless laughter or grimacing”<sup>30,46</sup>. These seizures are difficult to identify as the symptoms can easily been misinterpreted and the diagnosis if often delayed when the child develops other types of seizures<sup>32</sup> such as drop attacks, generalized tonic-clonic seizures, complex partial seizures, frequently associated with psychiatric disorders or cognitive impairment<sup>5,28,56</sup>. This evolution strongly suggests a secondary epileptogenesis that involves mainly frontal and temporal structures, strongly connected with hypothalamic region<sup>29,49</sup>. Since the first clinical description of a positive effect of hamartoma surgery on epilepsy<sup>53</sup>, many evidence of the implication of the lesion in the epileptic network have been provided in stereoelectroencephalography (SEEG)<sup>35,36,50</sup>. Beyond the strong evidence for the intrinsic epileptogenesis of the hamartomas strengthened by metabolic neuroimaging studies<sup>41,66</sup>, non-gelastic seizures may indicate an implication of temporal and frontal regions in the epileptic network<sup>67</sup>. These seizures can be independent from discharges from the hypothalamic hamartoma itself<sup>32</sup>. Alongside the description of the multiple aspects of the epileptic networks in hypothalamic hamartomas related epilepsy, many surgical techniques have been developed, including open, endoscopic and stereotactic techniques making it uneasy to have a clear overview of the available therapeutic possibilities.

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2 We conducted a narrative review of the surgical treatments of hypothalamic hamartomas by  
3 conducting a Pubmed/MEDLINE literature search up to November 2019 with the terms:  
4 'hypothalamic hamartoma', AND 'epilepsy', 'seizure', 'gelastic', 'precocious puberty',  
5 'secondary epileptogenesis', 'epileptic network'. We selected original papers with patients data  
6 based on their importance in the field.  
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## 11 12 13 14 **Focusing on the hamartoma** 15

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17 Hypothalamic hamartomas have a non-complex microarchitecture with many nodular groups  
18 of neurons of which 80% have an interneuron-like phenotype and express glutamic acid  
19 decarboxylase<sup>19</sup>. These neurons utilizing  $\gamma$ -aminobutyric acid as primary neurotransmitter have  
20 membrane features that make them have a spontaneous pacemaker-like firing activity. These  
21 predominant population of firing neurons is associated to large pleomorphic pyramidal neurons  
22 appearing to be excitatory projection having the functionally immature behavior of depolarizing  
23 and firing in response to GABA ligands<sup>40</sup>. These characteristics fit well with the hypothesis of  
24 a key role of hypothalamic hamartomas in the ictogenesis and the triggering of seizures that  
25 spread to a larger and diffuse epileptic network. This hypothesis has been strengthened by  
26 SEEG data<sup>35,36,50</sup>, and justifies the surgical development targeting directly the hypothalamic  
27 hamartoma.  
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38 However, hypothalamic hamartomas have also been considered as a model of human secondary  
39 epileptogenesis<sup>67</sup> at least for the two first stages according to the Morrel models : epileptiform  
40 discharges detected in the secondary focus were driven by the primary focus, whose destruction  
41 resulted in immediate cessation of epileptogenic discharges (first stage) ; independent seizures  
42 and interictal epileptiform discharges detected in the secondary focus that initially persist after  
43 removal of the primary focus, but eventually disappeared spontaneously later (second stage)<sup>77</sup>.  
44 This secondary epileptogenesis justifies an early surgical treatment of hypothalamic  
45 hamartoma related epilepsy and fits with the better seizure control reported in literature when  
46 surgery is precocious in the natural history of the disease<sup>26,37</sup>. Recent data suggested that the  
47 third stage, corresponding to a persistent long-term epileptiform activity in the secondary  
48 epileptogenic area after removal of the primary focus, may occur in hypothalamic hamartoma  
49 related epilepsy<sup>67</sup>. Consequently, phase I investigation suggesting a cingulate, a frontal or a  
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1 temporal independent network should make consider, especially in case of long medical history  
2 of epilepsy, to additionally and actively look for another ictal onset zone<sup>29,49,67</sup>.

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4 Independently from epilepsy, hypothalamic hamartomas have endocrine comorbidities<sup>31,46</sup>, the  
5 most common and frequently the only one being central precocious puberty. The main, but still  
6 unproven, physiopathology hypothesis is an ectopic generation and pulsatile release of  
7 gonadotropin-releasing hormone. This hypothesis relies on the possible production in the  
8 hypothalamic hamartoma of gonadotropin-releasing hormone regulators as transforming  
9 growth factor  $\alpha$  and  $\gamma$ -aminobutyric acid<sup>31</sup>. This hypothesis is strengthened by the reported  
10 efficiency of hypothalamic hamartoma resection to treat central precocious puberty<sup>47</sup>.  
11 Nevertheless, since GnRH agonists are widely available and effective, surgery should not be  
12 any more considered to treat isolated endocrine disturbances caused by hypothalamic  
13 hamartomas. That is why this review will focus on the epileptic control as objective of surgical  
14 treatment.  
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## 27 **Surgical techniques**

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29 Several surgical classifications have been proposed to orientate the best surgical approach and  
30 to predict the functional and epileptic outcome after the surgery. The original classification of  
31 1991 distinguishing the peduncular from the sessile hypothalamic hamartomas<sup>11</sup> was refined in  
32 two sub categories each by Valdueza (1a and 1b for peduncular and 2a and 2b for sessile  
33 hamartomas)<sup>76</sup>. Arita proposed a close classification that separates the parahypothalamic  
34 (usually the peduncular ones) from the intrahypothalamic (usually the sessile ones)  
35 hypothalamic hamartomas<sup>3</sup>. More complex classifications have been proposed, especially by  
36 Regis<sup>60</sup> and Shim<sup>70</sup>, but Delalande's classification into four subtypes<sup>22</sup> remains the most used<sup>46</sup>  
37 (Figure 1). Type I are small peduncular lesions characterized by an horizontal plane of  
38 attachment to the tuber cinereum ; Type II are mainly intraventricular lesions having a vertical  
39 plane of insertion ; Type III lesions are a combination of Types I and II having both an  
40 horizontal and a vertical insertion plane ; Type IV lesions are generally very large tumors with  
41 broad attachment to both the mammillary bodies and the hypothalamus and have an extension  
42 into the interpeduncular cistern.  
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### *Open disconnection and resection surgery*

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2 Since the first description of a surgical treatment of an hypothalamic hamartoma in 1969<sup>53</sup>, the  
3 discussion has been dominated by the opposition between two micro-neurosurgical techniques:  
4 one aiming to reach the lesion from below (pterional and transtemporal-transchoroidal  
5 approaches), versus another aiming to reach the lesion from above (transcallosal and  
6 transventricular)<sup>7,46,64</sup>. Whatever the technique (Figure 2), the possibility of complete removal  
7 is correlated to the importance of the attachment to the mamillary bodies (neuropsychological  
8 risk) and to the tuber cinereum (endocrine risk)<sup>62</sup>.  
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11 The pterional approach is the shortest and most direct route to the suprasellar cistern but the  
12 access to the third ventricle and the intraventricular component of the hypothalamic hamartoma  
13 is limited by the narrowness of the surgical corridor constituted by the carotid artery, optic nerve  
14 and chiasm, third cranial nerve, and infundibulum<sup>47</sup>. Although the reported seizure control is  
15 higher than 90% in some series, the morbidity is important, including transient third nerve  
16 palsy, thalamo-capsular infarcts, postoperative central diabetes insipidus, and hyperphagia.<sup>47</sup>  
17 These limits lead to the development of alternative surgical approaches reaching the lesion from  
18 above<sup>7,46,64</sup>. This technique was associated with good resection results for intraventricular  
19 lesions (Delalande Type II and IV) but remained limited in case of cisternal expansion of the  
20 lesion. In the review by Mittal and al. The complication rate reported was still high, the risk of  
21 memory impairment was increased<sup>47</sup>. Although new technologic advances have been used,  
22 including per-operative MRI, and succeeded in increasing the seizure free rate above 80%, the  
23 complication rate remains high, greater than 30%<sup>78</sup>. Concomitantly and with the similar  
24 objective to reach the lesion from above, a transcallosal transeptal interforaminal approach has  
25 been introduced in 2001<sup>63</sup> offering a wide exposition of the hypothalamic hamartoma. While the  
26 risk of cerebral infarction and oculomotor nerve palsy is reduced by avoiding manipulation of  
27 the vessels in the suprasellar and interpeduncular cistern, as well as the risk of injury to the  
28 mammillary bodies, pituitary stalk, the inherent risk is a fornical damage causing memory  
29 deficit<sup>48,52</sup>. Three large series totalizing 92 patients have been reported. Seizure frequency  
30 reduction was achieved in more than 90% and seizure freedom in between 50 to 55% of them.  
31 The most common complications were thalamic infarction and memory impairment (which was  
32 permanent in less than 10% of patients) but were counterbalanced by both cognitive and  
33 behavioral improvements (respectively 88% and 60% of patients). A correlation between  
34 completeness of excision of the hypothalamic hamartoma and seizure freedom have been  
35 demonstrated. Interestingly the memory impairment was higher in older patient, possibly as a  
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1 consequence from forniceal injury because the leaves of the septum pellucidum are not as easily  
2 separated<sup>47,52,78,83</sup>. In this context endoscopic approach has been introduced by Akai in 2002  
3 and then popularized by the Barrow Neurological Institute group from ~~2006~~<sup>2006</sup><sup>45</sup>. Between  
4 48% and 58% of patients of the two largest published series were seizure free<sup>18,51</sup> but major  
5 complications remain high<sup>51</sup> in one of them. To overcome this issue, the Cappabianca group  
6 proposed through a comprehensive review<sup>14</sup> to limit the endoscopic resection to the small  
7 hypothalamic hamartoma with a unilateral attachment to the hypothalamic wall with at least 6  
8 mm between the top of the lesion and the roof of the third ventricle.  
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### 10 *Stereotactic radiosurgery*

11 Stereotactic radiosurgery by Gamma Knife as a treatment of hypothalamic hamartomas was  
12 first reported in 1998 for a single young patient having a long history of hypothalamic  
13 hamartoma related drug resistant epilepsy<sup>4</sup>. The encouraging functional results of the treatment  
14 have been promptly followed by a series reported by Regis<sup>57</sup> and a prospective multicentric  
15 study in which 25Gy was delivered to the 50% isodose line<sup>58</sup>. Despite the usual delayed action  
16 of the radiosurgery, the results were very promising as only a minor complication happened (5  
17 months long hyperthermia) and 26% of patients were seizure free. The median number of  
18 seizures per month was reduce from 6.2 to 0.3. The median marginal dose was 17Gy (range, 14  
19 to 20). The long-term outcome on the study, in which 60 patients were enrolled, was published  
20 in 2006 and reported 31 patients with a minimum of three years follow up after the radiosurgery.  
21 The marginal isodose was 17Gy(range, 13 to 26) and beam blocking strategies was used to  
22 minimize the dose delivered to the frail structures surrounding the hypothalamic hamartoma  
23 (mammillary bodies, fornices, visual pathways, tuber cinereum and pituitary stalk)<sup>60</sup>. None of  
24 the patients presented permanent complications but 15% of them experienced a temporary  
25 worsening of seizures. 37% of patients were seizure free and another 22% had a significant  
26 reduction of seizures frequency. The best result was obtained in a patient having a small type  
27 II hypothalamic hamartoma.  
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29 Among the increasing literature evaluating radiosurgery since this first promising  
30 studies<sup>1,15,43,59-61</sup>, two level 2 prospective studies reported respectively 60%<sup>60</sup> and 66%<sup>43</sup> of  
31 seizure control following radiosurgery. Furthermore, a progressive positive effect on behavior  
32 during the 6 following months, co-occurring with sleep patterns and EEG normalization was  
33 described<sup>61</sup>. No major adverse event was reported, especially concerning the endocrine function  
34 <sup>15</sup>, except transient seizure control worsening and poikilothermia. More recently, these results  
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1 were strengthened by the publication of long term follow up of the study from the Marseille  
2 group<sup>59</sup>. Among the 57 patients investigated, 48 had a more than 3 years follow-up with a  
3 median follow-up of 71 months (range, 36 to 153). According to Delalande's classification, a  
4 single patient had a type I hypothalamic hamartoma, 26 a type II, 18 a type III and 3 a type IV.  
5 The median marginal dose was 17 Gy (range, 14 to 25) and the median target volume was 398  
6 mm<sup>3</sup> (range, 28 to 1600 mm<sup>3</sup>). 28 patients (58.3%) required a second treatment due to partial  
7 results. The rate of Engel class I outcome was 39.6%, Engel class II was 29.2%, and Engel class  
8 III was 20%. This result was associated with a cure of psychiatric comorbidity in 28% of  
9 patients, an improvement in 56%, a stable disease in 8% and a worsening in 8%. No permanent  
10 neurological side effect was reported especially with regard to memory deficit. 16.6% had a  
11 transient increase of the seizures frequency and transient poikilothermia was observed in 6.2%.  
12 14.5% required an additional open microsurgical treatment due to an insufficient efficacy.  
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22 The high level of endocrine safety of Gamma Knife radiosurgery has specifically been studied  
23 and reported a complication in only 1 of 34 treated patients (thyrotropin-stimulating hormone  
24 deficiency 2 years after the procedure)<sup>15</sup>.  
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28 These results, when compared to equivalent studies related to surgical approaches<sup>46</sup>, indicate  
29 comparable or better results for radiosurgery, with a reduced rate of adverse effects<sup>7,44</sup>.  
30 Nevertheless, no comparison has been conducted with the endoscopic or stereotactic approach  
31 recently developed to overcome the open microsurgery limits.  
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### 39 *Stereotactic laser interstitial thermotherapy*

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41 Laser interstitial thermotherapy (LiTT) consists in stereotactic placement of a laser probe  
42 through which a thermal lesion can be performed (Figure 3). The technique has initially been  
43 introduced in neuro-oncology as an alternative to open surgery<sup>45,69</sup> but has been adapted to  
44 epilepsy surgery as early as 1978<sup>33,39</sup>. Commercialization of LiTT coupled to MRI monitoring  
45 through the Visualase®<sup>81</sup> and the NeuroBlate®<sup>80</sup> system causes a growing interest for the  
46 technique and the multiplication of the publication of series.  
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53 As the technique requires a small diameter trephination through a tiny skin incision and a short  
54 stay at hospital, the technique is frequently presented as a minimally invasive technique.  
55 However, the complication rate in literature review, 3.4% of severe complications and 23.5%  
56 of overall complications<sup>34</sup>, does not differ from the reported rate in open epilepsy surgery<sup>65</sup>.  
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The recent introduction of this technique makes possible that this complication rate could be the result of a learning curve and could be expected to decrease in time. In the context of a high potential of this technique in epilepsy surgery, specific series on hypothalamic hamartomas have been published (Figure 4).

The University of California in San Francisco group introduced the technique and reported a seizure free rate of 60% associated to 20% of adverse effects on a series of 5 patients<sup>73</sup>. A first large literature review<sup>81</sup> on 22 procedures with a mean follow-up of 17.4 months revealed that 80% of patients having gelastic seizures were seizure free after treatment and 56% of other patients had the same results. Immediate complication rate was 39% and 22% of patients had a permanent deficit, including hypothyroidism, short-term memory loss and weight gain. More recently, very experienced teams started publishing their results on large single center series. The series of the Texas Children's Hospital reported 71 patients. Among patients having more than one year follow-up, 78% were free of gelastic seizures and 12% were seizure free. 20% of patients needed a repeated treatment. The complication rate was 5.4%<sup>20</sup>. The Northwell Hospital group in New York reported a series of 8 patients and obtained a seizure free rate of 75% and a permanent complication rate of 12.5%<sup>24</sup>.

Interestingly, the Barrow Neurological Institute group at Phoenix Children's Hospital developed a strategy going further than anatomical targeting for the LiTT in hypothalamic hamartomas (Figure 4)<sup>6</sup>. Although all neurons within the lesion are abnormal, some of them do not communicate outside of the hypothalamic hamartoma, so it was suggested that a lesioning of the whole hypothalamic hamartoma may be unnecessary. In addition to the anatomical localization of the lesion, data obtained by functional fMRI were taken into account. These data corresponded to the whole-brain functional connectivity of every individual hypothalamic hamartoma voxel. Images that showed connectivity between the hypothalamic hamartoma and any portion of the rest of the brain were considered as a part of the epileptic network. Subcentimeter targets obtained by resting state fMRI were then defined. The results of this approach have been reported through a 51 patients controlled study including 15 control patients and 36 patients undergoing the above described procedure. Results were significantly better in the fMRI targeted group (overall seizure reduction 85%, Engel I 92%) than in the control group (overall seizure reduction 49%, Engel I 45%). No postoperative morbidity or mortality occurred in the fMRI targeted group.

1 This approach improved freedom from seizures by 45% compared to conventional ablation,  
2 regardless of hamartoma size, and reduced morbidity compared to other recent studies which  
3 reach 20% permanent significant morbidity.  
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### 8 *Stereotactic radiofrequency coagulation* 9

10 Stereotactic radiofrequency thermocoagulation in epilepsy surgery has been introduced during  
11 the second half of the XX<sup>th</sup> century<sup>68</sup> originally for the treatment of temporal lobe epilepsy. The  
12 extension of this technique to the specific indication of hypothalamic hamartomas is more  
13 recent<sup>37,42,54</sup>.  
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18 The most important contribution in this area comes from the Nishi-Niigata group in Japan<sup>37</sup>  
19 who reported 140 consecutive procedures of MRI-guided stereotactic radiofrequency  
20 thermocoagulation for hypothalamic hamartomas over 100 patients (Figure 4). The median  
21 follow-up was 3 years (range, 1 to 17) and only 10% of patients had pure gelastic seizures. 86%  
22 of patients were free of gelastic seizures and the overall seizure freedom rate was 71%. This  
23 result was obtained with a median of 4 trajectories (range, 1 to 10) and 6 lesions (range, 1-36)  
24 per procedure. Permanent endocrine deficit concerned 2% of patients and required replacement  
25 therapy for hypocortisolism, hypothyroidism or diabetes insipidus. The rate of transient  
26 complications was high with 60.0% of Horner's syndrome, 27.9% of hyperphagia, 22.1% of  
27 hyponatremia, 22.1% of hyperthermia, 8.6% of short-term memory disturbance, 0.7% of  
28 disturbance of consciousness. 32% of patients required multiple procedures. It is worth noticing  
29 that the cognitive outcome has been specifically studied and was improved after stereotactic  
30 radiofrequency coagulation of the hamartoma<sup>72</sup>. Similar results were reported in 2003 in a series  
31 of 12 children<sup>42</sup> (but 6 patients underwent simultaneously an endoscopic treatment making the  
32 results hardly comparable) and in a series of 5 patients<sup>74</sup>.  
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47 More recently and similarly to the functional connectivity approach developed for the super-  
48 selective LiTT treatment<sup>6</sup>, SEEG-guided radiofrequency-thermocoagulation (SEEG-guided  
49 RF-TC) has been proposed for the hypothalamic hamartoma treatment<sup>79</sup>. SEEG-guided RF-TC  
50 consists of coupling SEEG investigation with RF-TC stereotactic lesioning directly through the  
51 recording electrodes<sup>10</sup> and is valuable in epilepsy surgery<sup>9</sup>, especially to treat periventricular  
52 nodular heterotopia<sup>8</sup>, a pathology sharing a lot of similarities with hypothalamic hamartoma.  
53 Over a series of 9 patients, results were in the same range than conventional stereotactic  
54 radiofrequency coagulation<sup>79</sup>. However, such an indication requires to be carefully justified, as  
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2 phase II investigations can be unnecessary to investigate hypothalamic hamartoma related  
3 seizures.  
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### 6 *Endoscopic laser and radiofrequency coagulation treatment*

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9 Robot assisted endoscopy to perform hypothalamic hamartomas disconnection as an alternative  
10 to the microsurgical removal and stereotactic destruction of the lesions was introduced in 2003  
11 by Delalande<sup>22,27</sup>. Surgical excision of the lesion has indeed no interest from an oncological  
12 point of view and a disconnection, except for type I hypothalamic hamartoma, can be achieved  
13 less invasively by an endoscopic trans-ventricular approach<sup>23</sup>. Stereotactic lesions, either by  
14 LiTT or RF-TC, are also less invasive than open microsurgical technique but a probe can only  
15 produce a spherical or an oblong lesion. Hypothalamic hamartomas are not always a perfect fit  
16 with this volume and the attachment to the functional adjacent hypothalamic structure is usually  
17 planar. It could be difficult to obtain a safe and complete disconnection of such planar insertion  
18 by performing a curved lesion with a single trajectory. That is why multiple probe stereotactic  
19 placement have been proposed<sup>71</sup>. To overcome the necessity to perform multiple stereotactic  
20 trajectory, the endoscopic robot assisted approach, allow to perform a single intraparenchymal  
21 trajectory, known to be functionally safe, and to perform multiple intraventricular placements  
22 of a RF-TC<sup>22</sup> or laser<sup>13</sup> probe. Such flexibility in probe placement make it possible to perform  
23 multiple small volume lesions of the attachment plan of the hamartoma, which make  
24 conceptually this technique safer regarding the function of the adjacent structure (Figure 4,  
25 Video 1 & 2).  
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41 Efficacy and safety of this original approach has recently been reported through a large series  
42 reporting long term outcome<sup>25,26</sup>. Over the 136 patients reported<sup>25</sup>, 112 were children<sup>26</sup> among  
43 whom 2 were type I, 67 were type II, 31 were type III and 12 were type IV, according to  
44 Delalande's classification. The median follow-up was 4 years. For all hypothalamic hamartoma  
45 types, 77.6% of the patients had a favorable outcome (Engel 1+2 outcome score) with 57.1%  
46 seizure-free (Engel 1). The best outcome was obtained in patients with type 2 hypothalamic  
47 hamartomas, (68.7% Engel 1 and 85.1% Engel 1+2), which is in line with previous series.  
48 Patients with isolated gelastic seizures had a better outcome (Engel 1+2 in 90%), as compared  
49 to those with other seizure types. Unsurprisingly, a short delay between hamartoma diagnosis  
50 and surgery was a factor for a good outcome. Similarly to stereotactic techniques, multiple  
51 procedures were frequently needed to achieve good results. The mean number of procedures  
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1 required depended on the Delalande type: 1.50 for type I ; 1.52 for type II ; 1.84 for type III ;  
2 2.46 for type IV.  
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4 The overall complication rate was 8.3%, which is similar to available literature.  
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## 8 **Conclusion** 9

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11 Surgery is the most effective treatment for drug resistant hypothalamic hamartoma related  
12 epilepsy and has to be as precocious as possible, regardless the technique<sup>20,26,37</sup>. Although open  
13 microsurgical resection leads to good epileptological outcomes, its high complication rate limits  
14 indications. Only Delalande's type I purely cisternal peduncular forms, when associated with  
15 drug-resistant epilepsy, remain a good indications to perform pterional approach<sup>23,47</sup>. Laser and  
16 radiofrequency coagulation procedures (Figure 4) are significant advances compared to the  
17 historical microsurgical procedures. Concerning the approaches making a lesion to the whole  
18 hypothalamic hamartoma, literature review suggests that multiple radiofrequency small  
19 lesions<sup>37</sup> have a better efficacy and safety than LiTT<sup>20,34</sup>, probably due to the difficulty of the  
20 latter technique to target the whole lesion while sparing the adjacent structures (Figure 4).  
21 Nevertheless, these statement is based on single center results and will probably be  
22 counterbalanced by the recent advances of super-selective lesions performed with LiTT<sup>82</sup>.  
23 Disconnection approach by laser and radiofrequency coagulation in robot guided stereo-  
24 endoscopy provides very good results in term of seizure control and safety, probably due to  
25 possibility to fully disconnect the lesion and to spare the adjacent structures by a planar section  
26 (Figure 4)<sup>25,26</sup>.  
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41 Going beyond the surgical technique, the analysis of the pathological functional connectivity  
42 of the hypothalamic hamartoma by resting state MRI made it possible to target a subpart of the  
43 lesion<sup>6</sup>. This approach coupled with LiTT procedures showed excellent results in term of  
44 seizure control and safety (Figure 4)<sup>6</sup>. These findings suggest that the true impact on the surgical  
45 results does not come from purely surgical technique (laser vs radiofrequency coagulation or  
46 stereotactic vs robot-guided stereo-endoscopy) but relies on the understanding of the epileptic  
47 network, including inside the epileptic hamartoma, that makes possible to plan a disconnection  
48 or a lesioning that spare the adjacent functional structures.  
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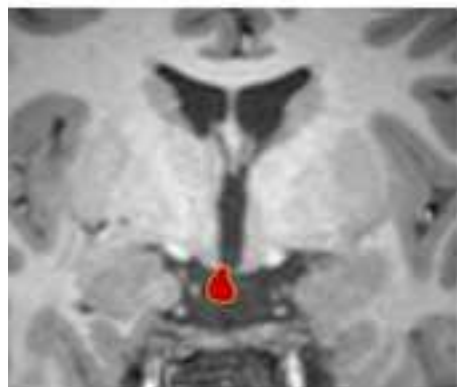
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	Rounded seizure control rate	Rounded seizure free rate	Rounded complication rate	Rounded number of patients reported	Main type of complication
Pterional approach <sup>51,67</sup>	90%	55%	50%	30	Third nerve palsy Hemiplegia Diabetes insipidus Hyperphagia Memory impairment
Transcallosal approach <sup>51,55,65</sup>	90%	50-55%	10%	70	Memory impairment Thalamic infarction
Endoscopic resection <sup>2,19,45,54</sup>	80%	45-50%	8%	25	Memory impairment Hemiparesis
Stereotactic radiosurgery <sup>16,47,60</sup>	65%	25%	0%	80	-
LiTT (standard) <sup>21,22,85</sup>	80%	45%	25%	115	Memory impairment Hyperphagia
LiTT (fMRI targeted) <sup>6</sup>	90%	90%	0%	35	-
Stereotactic RF-TC <sup>39</sup>	80%	70%	2%	100	Diabetes insipidus
Endoscopic laser and RF-TC <sup>28</sup>	80%	60%	8%	135	Diabetes insipidus Hemiplegia Third nerve palsy

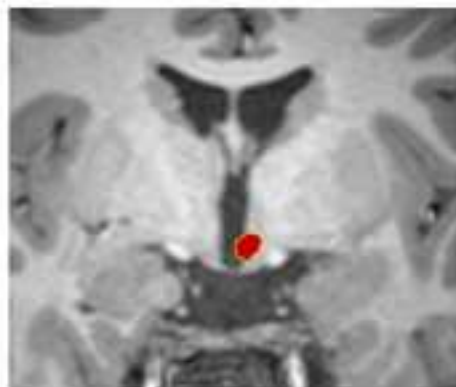
Table 1: overview of the different surgical approaches for the treatment of hypothalamic hamartomas. Rates and numbers are rounded based on the literature. Exact rates are described in the respective sections. RF-TC: radiofrequency thermocoagulation; LiTT: laser interstitial thermotherapy.



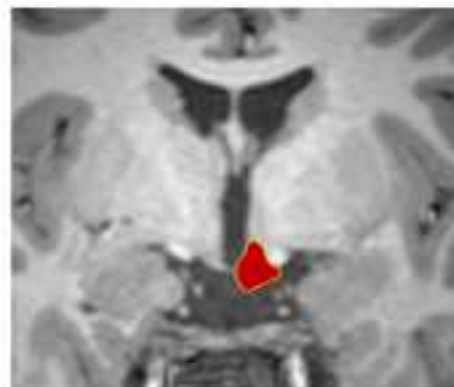
**Type I**



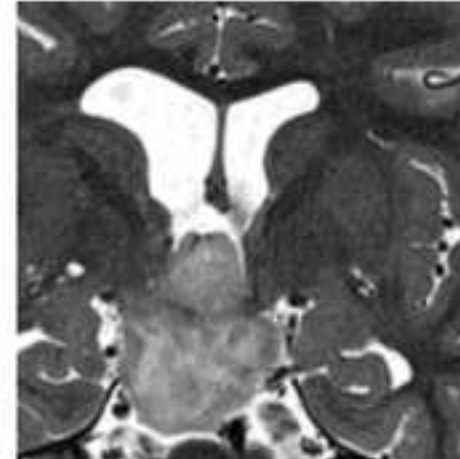
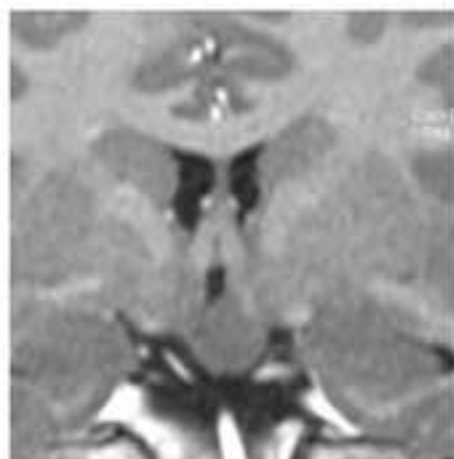
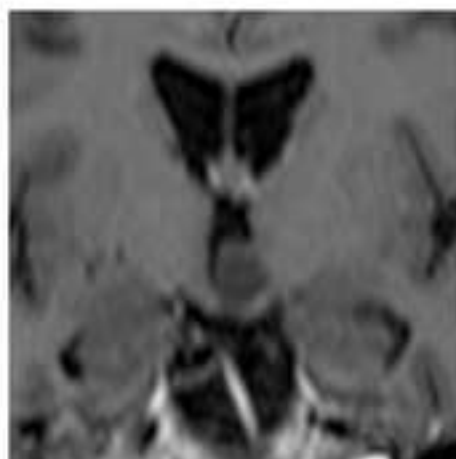
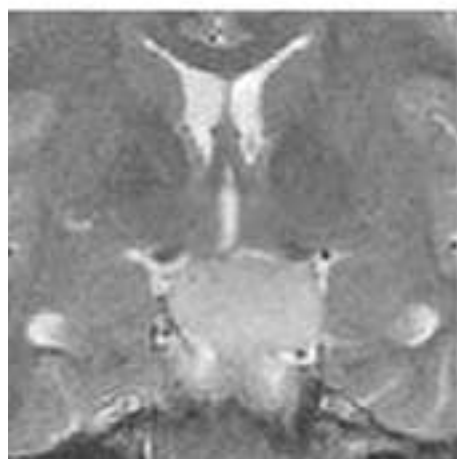
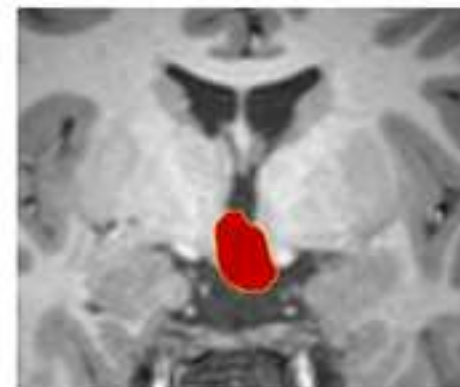
**Type II**



**Type III**



**Type IV**



Pterional Approach

Transventricular Approach

Transcallosal Approach

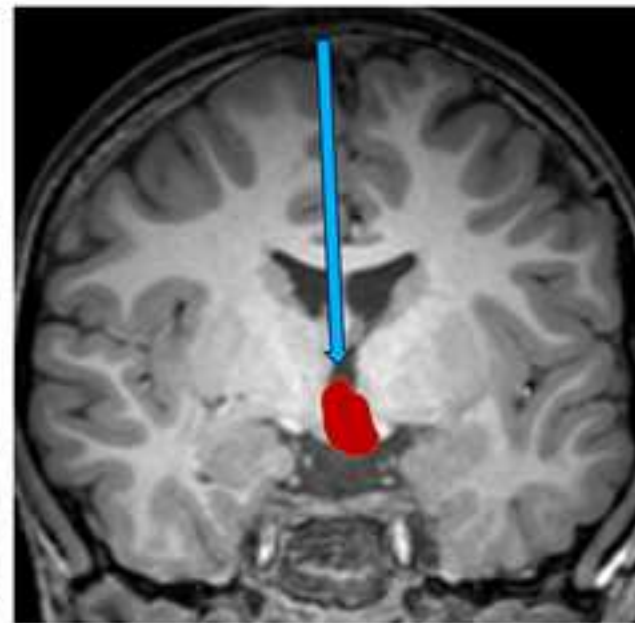
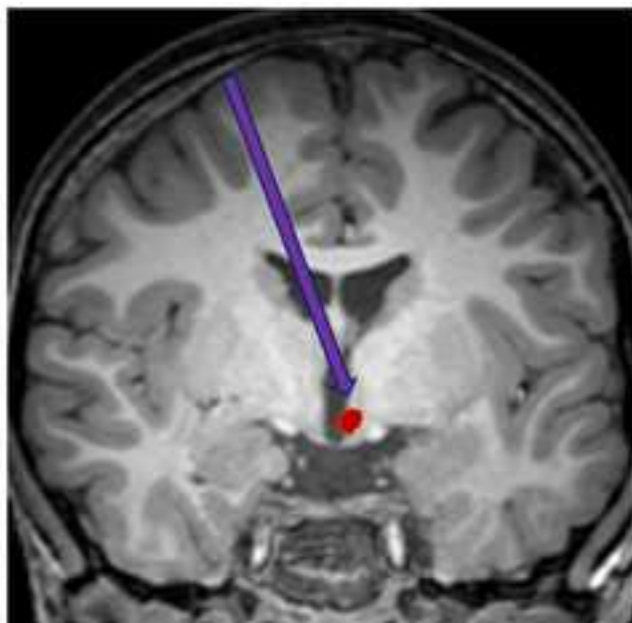
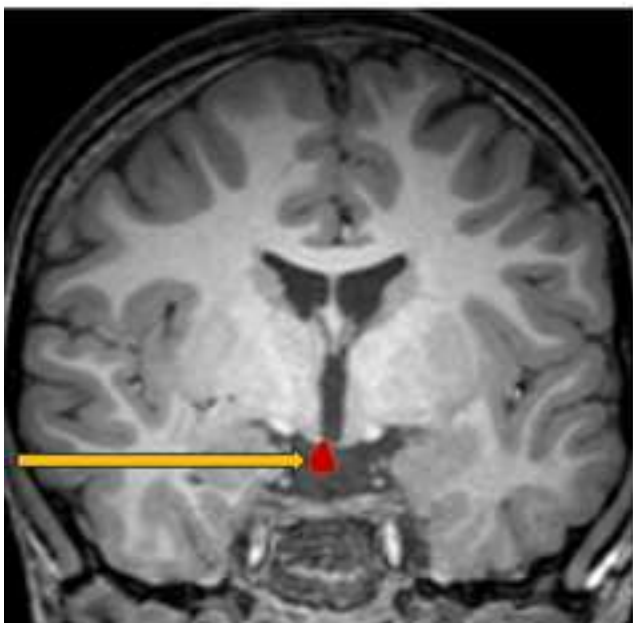
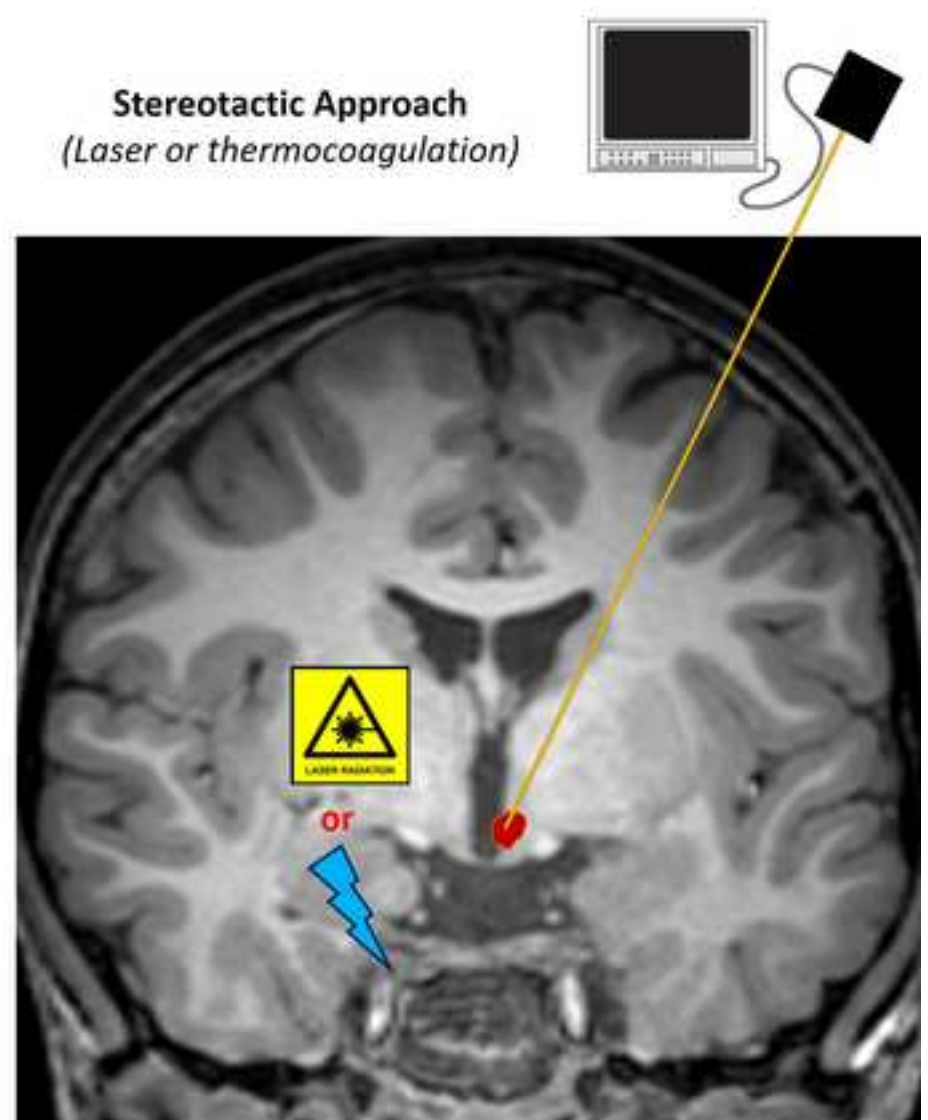
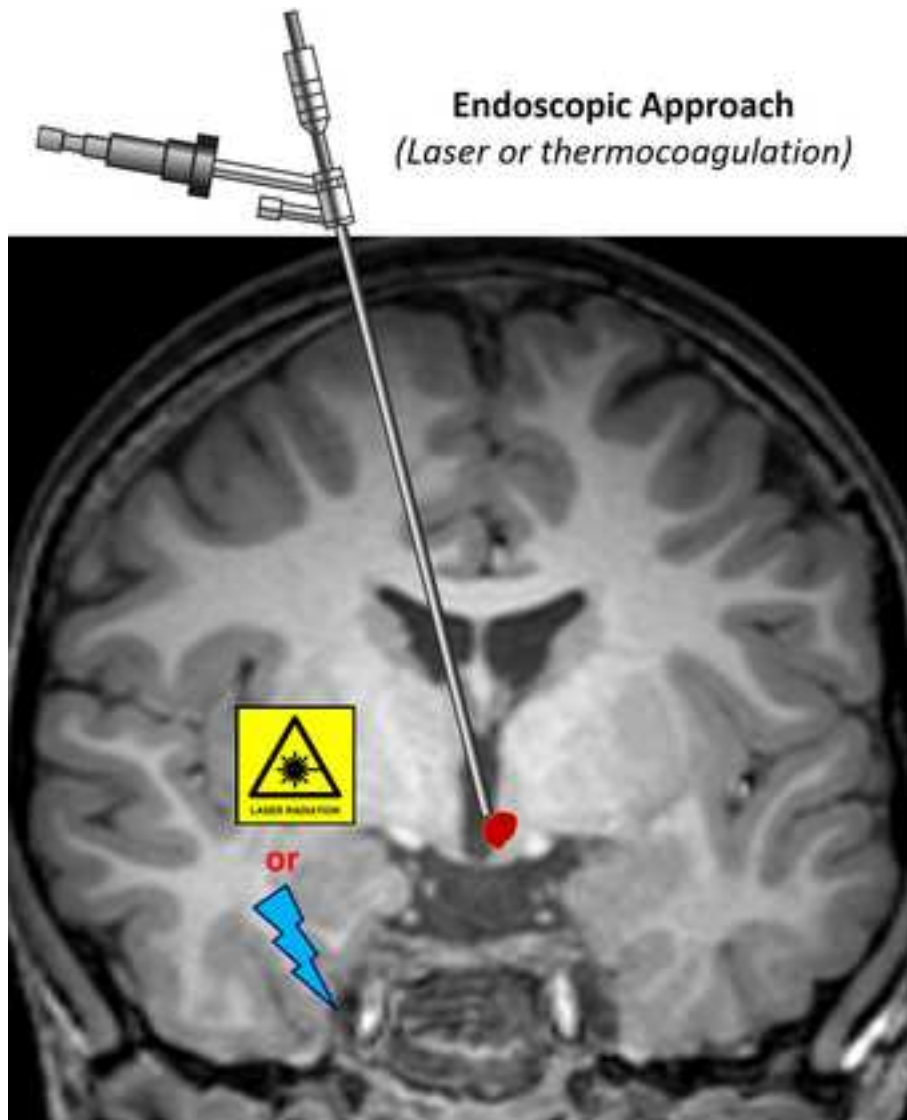
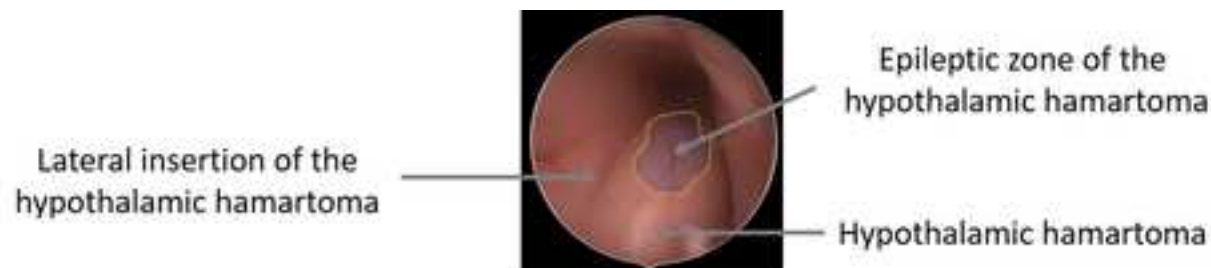


Figure 2.jpg





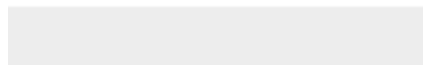
	<p><b>Single lesion</b> (Laser - stereotactic)</p>	<p>A stereotactic lesion is performed through a single trajectory. The shape of the lesion (red) make hardly avoidable to spare adjacent structures (dark red) when the whole hamartoma is targeted.</p>	<p>Xu &amp; al. 2018 Curry &amp; al. 2018 Hoppe &amp; al. 2018</p>
	<p><b>Multiple lesions</b> (Radiofrequency coagulation - stereotactic)</p>	<p>Multiple stereotactic stereotactic lesions are preformed through multiple trajectories making easier to spare the adjacent structures bur requiring multiple electrode insertions.</p>	<p>Kameyama &amp; al. 2016</p>
	<p><b>Disconnection</b> (Laser / Radiofrequency coagulation – robot guided stereo-endoscopy)</p>	<p>A planar disconnection is performed along the insertion of the hamartoma. Endoscopy allow to perform multiple/linear lesions trough a single intraparenchymal robot guided trajectory.</p>	<p>Ferrand-Sorbet &amp; al. 2020</p>
	<p><b>Single lesion with epileptic zone targeting</b> (Laser- stereotactic)</p>	<p>The epileptic zone within the hamartoma (yellow circled blue zone) is identified by resting state connectivity fMRI. A stereotactic lesion is performed through a single trajectory. The limited volume of the lesion make possible to spare the adjacent structures.</p>	<p>Boerwinkle &amp; al. 2018</p>



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**Video**

**Thermocoag Hamartomas.mov**





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