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.

Introduction

Hypothalamic hamartomas (from ἁμαρτία, sin) are rare heterotopic masses resulting from an aberrant development of normal tissue that arise from the ventral hypothalamus[40]. They are composed of abnormally distributed but cytologically normal neurons and glia, including fibrillary astrocytes and oligodendrocytes [19,46]. 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[38]. These developmental malformations can be diagnosed incidentally[16] or during investigation of neurological, psychiatric or endocrine disturbances[46] 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[17]. Epilepsy and behavioral or cognitive disorders are associated with hypothalamic hamartomas connected with the mamillary bodies[55,76]. Epilepsy usually starts during the first year of life with the classical gelastic seizures[46] (from γέλως, laugh) or less frequently dacrystic (from δάκρυ, tear) seizures[12]. These very specific seizures have first been reported during the late XIXth century by Armand Trousseau[75] as an "irrepressible pulsion to laugh". The term "gelastic" was introduced in 1957[21], and description of gelastic attacks defined in 1971 as "characterized by repeated short-lasting seizures with initial emotionless laughter or grimacing"[30,46]. 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[32] such as drop attacks, generalized tonico-clonic seizures, complex partial seizures, frequently associated with psychiatric disorders or cognitive impairement[5,28,56]. This evolution strongly suggests a secondary epileptogenesis that involves mainly frontal and temporal structures, strongly connected with hypothalamic region[29,49]. Since the first clinical description of a positive effect of hamartoma surgery on epilepsy[53], many evidence of the implication of the lesion in the epileptic network have been provided in stereoelectroencephalography (SEEG)[35,36,50]. Beyond the strong evidence for the intrinsic epileptogenesis of the hamartomas strengthened by metabolic neuroimaging studies[41,66], non-gelastic seizures may indicate an implication of temporal and frontal regions in the epileptic network[67]. These seizures can be independent from discharges from the hypothalamic hamartoma itself[32]. 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.

We conducted a narrative review of the surgical treatments of hypothalamic hamartomas by conducting a Pubmed/MEDLINE literature search up to November 2019 with the terms: 'hypothalamic hamartoma', AND 'epilepsy', 'seizure', 'gelastic', 'precocious puberty', 'secondary epileptogenesis', 'epileptic network'. We selected original papers with patients data based on their importance in the field.

Focusing on the hamartoma

Hypothalamic hamartomas have a non-complex microarchitecture with many nodular groups of neurons of which 80% have an interneuron-like phenotype and express glutamic acid decarboxylase [19]. These neurons utilizing γ-aminobutyric acid as primary neurotransmitter have membrane features that make them have a spontaneous pacemaker-like firing activity. These predominant population of firing neurons is associated to large pleomorphic pyramidal neurons appearing to be excitatory projection having the functionally immature behavior of depolarizing and firing in response to GABA ligands[40]. These characteristics fit well with the hypothesis of a key role of hypothalamic hamartomas in the ictogenesis and the triggering of seizures that spread to a larger and diffuse epileptic network. This hypothesis has been strengthened by SEEG data[35,36,50], and justifies the surgical development targeting directly the hypothalamic hamartoma.

However, hypothalamic hamartomas have also been considered as a model of human secondary epileptogenesis[67] at least for the two first stages according to the Morrel models : epileptiform discharges detected in the secondary focus were driven by the primary focus, whose destruction resulted in immediate cessation of epileptogenic discharges (first stage) ; independent seizures and interictal epileptiform discharges detected in the secondary focus that initially persist after removal of the primary focus, but eventually disappeared spontaneously later (second stage)[77]. This secondary epileptogenesis justifies an early surgical treatment of hypothalamic hamartoma related epilepsy and fits with the better seizure control reported in literature when surgery is precocious in the natural history of the disease[26,37]. Recent data suggested that the third stage, corresponding to a persistent long-term epileptiform activity in the secondary epileptogenic area after removal of the primary focus, may occur in hypothalamic hamartoma related epilepsy[67]. Consequently, phase I investigation suggesting a cingulate, a frontal or a

temporal independent network should make consider, especially in case of long medical history of epilepsy, to additionally and actively look for another ictal onset zone[29,49,67].

Independently from epilepsy, hypothalamic hamartomas have endocrine comorbidities[31,46], the most common and frequently the only one being central precocious puberty. The main, but still unproven, physiopathology hypothesis is an ectopic generation and pulsatile release of gonadotropin-releasing hormone. This hypothesis relies on the possible production in the hypothalamic hamartoma of gonadotropin-releasing hormone regulators as transforming growth factor α and γ-aminobutyric acid[31]. This hypothesis is strengthened by the reported efficiency of hypothalamic hamartoma resection to treat central precocious puberty[47]. Nevertheless, since GnRH agonists are widely available and effective, surgery should not be any more considered to treat isolated endocrine disturbances caused by hypothalamic hamartomas. That is why this review will focus on the epileptic control as objective of surgical treatment.

Surgical techniques

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

Open disconnection and resection surgery

Since the first description of a surgical treatment of an hypothalamic hamartoma in 1969 [53], the discussion has been dominated by the opposition between two micro-neurosurgical techniques: one aiming to reach the lesion from below (pterional and transtemporal-transchoroidal approaches), versus another aiming to reach the lesion from above (transcallosal and transventricular)[7,46,64]. Whatever the technique (Figure 2), the possibility of complete removal is correlated to the importance of the attachment to the mamillary bodies (neuropsychological risk) and to the tuber cinereum (endocrine risk)[62].

The pterional approach is the shortest and most direct route to the suprasellar cistern but the access to the third ventricle and the intraventricular component of the hypothalamic hamartoma is limited by the narrowness of the surgical corridor constituted by the carotid artery, optic nerve and chiasm, third cranial nerve, and infundibulum[47]. Although the reported seizure control is higher than 90% in some series, the morbidity is important, including transient third nerve palsy, thalamo-capsular infarcts, postoperative central diabetes insipidus, and hyperphagia.[47] These limits lead to the development of alternative surgical approaches reaching the lesion from above[7,46,64]. This technique was associated with good resection results for intraventricular lesions (Delalande Type II and IV) but remained limited in case of cisternal expension of the lesion. In the review by Mittal and al. The complication rate reported was still high, the risk of memory impairment was increased[47]. Although new technologic advances have been used, including per-operative MRI, and succeded in increasing the seizure free rate above 80%, the complication rate remains high, greater than 30%[78]. Concomitantly and with the similar objective to reach the lesion from above, a transcallosal transeptal interfornical approach has been introduce in 2001[63] offering a wide exposition of the hypothalamic hamartoma. While the risk of cerebral infarction and oculomotor nerve palsy is reduced by avoiding manipulation of the vessels in the suprasellar and interpeduncular cistern, as well as the risk of injury to the mammillary bodies, pituitary stalk, the inherent risk is a fornical damage causing memory deficit[48,52]. Three larges series totalizing 92 patients have been reported. Seizure frequency reduction was acheved in more than 90% and seizure freedom in between 50 to 55% of them. The most common complications were thalamic infarction and memory impairement (wich was permanent in less than 10% of patients) but were conterbalanced by both cognitive and behavhioral improvements (respectively 88% and 60% of patients). A correlation between completeness of excision of the hypothalamic hamartoma and seizure freedom have been demonstrated. Interestingly the memory impairement was higher in older patient, possibly as a

consequence from forniceal injury because the leaves of the septum pellucidum are not as easily separated[47,52,78,83]. In this context endoscopic approach has been introduced by Akai in 2002 and then popularized by the Barrow Neurological Institute group from 2006[2]~~2006[45]~~. Between 48% and 58% of patients of the two largest published series were seizure free[18,51] but major complications remain high[51] in one of them. To overcome this issue, the Cappabianca group proposed through a comprehensive review[14] to limit the endoscopic resection to the small hypothalamic hamartoma with a unilateral attachment to the hypothalamic wall with at least 6 mm between the top of the lesion and the roof of the third ventricle.

Stereotactic radiosurgery

Stereotactic radiosurgery by Gamma Knife as a treatment of hypothalamic hamartomas was first reported in 1998 for a single young patient having a long history of hypothalamic hamartoma related drug resistant epilepsy[4]. The encouraging functional results of the treatment have been promptly followed by a series reported by Regis[57] and a prospective multicentric study in which 25Gy was delivered to the 50% isodose line[58]. Despite the usual delayed action of the radiosurgery, the results were very promising as only a minor complication happened (5 months long hyperthermia) and 26% of patients were seizure free. The median number of seizures per month was reduce from 6.2 to 0.3. The median marginal dose was 17Gy (range, 14 to 20). The long-term outcome on the study, in which 60 patients were enrolled, was published in 2006 and reported 31 patients with a minimum of three years follow up after the radiosurgery. The marginal isodose was 17Gy(range, 13 to 26) and beam blocking strategies was used to minimize the dose delivered to the frail structures surrounding the hypothalamic hamartoma (mammillary bodies, fornices, visual pathways, tuber cinereum and pituitary stalk)[60]. None of the patients presented permanent complications but 15% of them experienced a temporary worsening of seizures. 37% of patients were seizure free and another 22% had a significant reduction of seizures frequency. The best result was obtained in a patient having a small type II hypothalamic hamartoma.

Among the increasing literature evaluating radiosurgery since this first promising studies[1,15,43,59–61], two level 2 prospective studies reported respectively 60% [60] and 66% [43] of seizure control following radiosurgery. Furthermore, a progressive positive effect on behavior during the 6 following months, co-occurring with sleep patterns and EEG normalization was described[61]. No major adverse event was reported, especially concerning the endocrine function [15], except transient seizure control worsening and poikilothermia. More recently, these results

were strengthened by the publication of long term follow up of the study from the Marseille group[59]. Among the 57 patients investigated, 48 had a more than 3 years follow-up with a median follow-up of 71 months (range, 36 to 153). According to Delalande's classification, a single patient had a type I hypothalamic hamartoma, 26 a type II, 18 a type III and 3 a type IV. The median marginal dose was 17 Gy (range,14 to 25) and the median target volume was 398 mm^3 (range, 28 to 1600 mm^3). 28 patients (58.3%) required a second treatment due to partial results. The rate of Engel class I outcome was 39.6%, Engel class II was 29.2%, and Engel class III was 20%. This result was associated with a cure of psychiatric comorbidity in 28% of patients, an improvement in 56%, a stable disease in 8% and a worsening in 8%. No permanent neurological side effect was reported especially with regard to memory deficit. 16.6% had a transient increase of the seizures frequency and transient poikilothermia was observed in 6.2%. 14.5% required an additional open microsurgical treatment due to an insufficient efficacy.

The high level of endocrine safety of Gamma Knife radiosurgery has specifically been studied and reported a complication in only 1 of 34 treated patients (thyrotropin-stimulating hormone deficiency 2 years after the procedure)[15].

These results, when compared to equivalent studies related to surgical approaches [46], indicate comparable or better results for radiosurgery, with a reduced rate of adverse effects [7,44]. Nevertheless, no comparison has been conducted with the endoscopic or stereotactic approach recently developed to overcome the open microsurgery limits.

Stereotactic laser interstitial thermotherapy

Laser interstitial thermotherapy (LiTT) consists in stereotactic placement of a laser probe through which a thermal lesion can be performed (Figure 3). The technique has initially been introduced in neuro-oncology as an alternative to open surgery[45,69] but has been adapted to epilepsy surgery as early as 1978[33,39]. Commercialization of LiTT coupled to MRI monitoring through the Visualase®[81] and the NeuroBlate®[80] system causes a growing interest for the technique and the multiplication of the publication of series.

As the technique requires a small diameter trephination through a tiny skin incision and a short stay at hospital, the technique is frequently presented as a minimally invasive technique. However, the complication rate in literature review, 3.4% of severe complications and 23.5% of overall complications[34], does not differ from the reported rate in open epilepsy surgery[65].

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[73]. A first large literature review[81] 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%[20]. 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%[24].

Interestingly, the Barrow Neurological Institute group at Phoenix Children's Hospital developped a strategy going further than anatomical targeting for the LiTT in hypothalamic hamartomas (Figure 4)[6]. 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.

This approach improved freedom from seizures by 45% compared to conventional ablation, regardless of hamartoma size, and reduced morbidity compared to other recent studies which reach 20% permanent significant morbidity.

Stereotactic radiofrequency coagulation

Stereotactic radiofrequency thermocoagulation in epilepsy surgery has been introduced during the second half of the XXth century[68] originally for the treatment of temporal lobe epilepsy. The extension of this technique to the specific indication of hypothalamic hamartomas is more recent[37,42,54].

The most important contribution in this area comes from the Nishi-Niigata group in Japan[37] who reported 140 consecutive procedures of MRI-guided stereotactic radiofrequency thermocoagulation for hypothalamic hamartomas over 100 patients (Figure 4). The median follow-up was 3 years (range, 1 to17) and only 10% of patients had pure gelastic seizures. 86% of patients were free of gelastic seizures and the overall seizure freedom rate was 71%. This result was obtained with a median of 4 trajectories (range, 1 to 10) and 6 lesions (range, 1-36) per procedure. Permanent endocrine deficit concerned 2% of patients and required replacement therapy for hypocortisolism, hypothyroidism or diabetes insipidus. The rate of transient complications was high with 60.0% of Horner's syndrome, 27.9% of hyperphagia, 22.1% of hyponatremia, 22.1% of hyperthermia, 8.6% of short-term memory disturbance, 0.7% of disturbance of consciousness. 32% of patients required multiple procedures. It is worth noticing that the cognitive outcome has been specifically studied and was improved after stereotactic radiofrequency coagulation of the hamartoma[72]. Similar results were reported in 2003 in a series of 12 children[42] (but 6 patients underwent simultaneously an endoscopic treatment making the results hardly comparable) and in a series of 5 patients[74].

More recently and similarly to the functional connectivity approach developed for the super-selective LiTT treatment[6], SEEG-guided radiofrequency-thermocoagulation (SEEG-guided RF-TC) has been proposed for the hypothalamic hamartoma treatment[79]. SEEG-guided RF-TC consists of coupling SEEG investigation with RF-TC stereotactic lesioning directly through the recording electrodes[10] and is valuable in epilepsy surgery[9], especially to treat periventricular nodular heterotopia[8], a pathology sharing a lot of similarities with hypothalamic hamartoma. Over a series of 9 patients, results were in the same range than conventional stereotactic radiofrequency coagulation[79]. However, such an indication requires to be carefully justified, as

phase II investigations can be unnecessary to investigate hypothalamic hamartoma related seizures.

Endoscopic laser and radiofrequency coagulation treatment

Robot assisted endoscopy to perform hypothalamic hamartomas disconnection as an alternative to the microsurgical removal and stereotactic destruction of the lesions was introduced in 2003 by Delalande[22,27]. Surgical excision of the lesion has indeed no interest from an oncological point of view and a disconnection, except for type I hypothalamic hamartoma, can be achieved less invasively by an endoscopic trans-ventricular approach[23]. Stereotactic lesions, either by LiTT or RF-TC, are also less invasive than open microsurgical technique but a probe can only produce a spherical or an oblong lesion. Hypothalamic hamartomas are not always a perfect fit with this volume and the attachment to the functional adjacent hypothalamic structure is usually planar. It could be difficult to obtain a safe and complete disconnection of such planar insertion by performing a curved lesion with a single trajectory. That is why multiple probe stereotactic placement have been proposed[71]. To overcome the necessity to perform multiple stereotactic trajectory, the endoscopic robot assisted approach, allow to perform a single intraparenchymal trajectory, known to be functionally safe, and to perform multiple intraventricular placements of a RF-TC[22] or laser[13] probe. Such flexibility in probe placement make it possible to perform multiple small volume lesions of the attachment plan of the hamartoma, which make conceptually this technique safer regarding the function of the adjacent structure (Figure 4, Video 1 & 2).

Efficacy and safety of this original approach has recently been reported through a large series reporting long term outcome[25,26]. Over the 136 patients reported[25], 112 were chidren[26] among whom 2 were type I, 67 were type II, 31 were type III and 12 were type IV, according to Delalande's classification. The median follow-up was 4 years. For all hypothalamic hamartoma types, 77.6% of the patients had a favorable outcome (Engel 1+2 outcome score) with 57.1% seizure-free (Engel 1). The best outcome was obtained in patients with type 2 hypothalamic hamartomas, (68.7% Engel 1 and 85.1% Engel 1+2), which is in line with previous series. Patients with isolated gelastic seizures had a better outcome (Engel 1+2 in 90%), as compared to those with other seizure types. Unsurprisingly, a short delay between hamartoma diagnosis and surgery was a factor for a good outcome. Similarly to stereotactic techniques, multiple procedures were frequently needed to achieve good results. The mean number of procedures

required depended on the Delalande type: 1.50 for type I ; 1.52 for type II ; 1.84 for type III ; 2.46 for type IV.

The overall complication rate was 8.3%, which is similar to available literature.

Conclusion

Surgery is the most effective treatment for drug resistant hypothalamic hamartoma related epilepsy and has to be as precocious as possible, regardless the technique[20,26,37]. Although open microsurgical resection leads to good epileptological outcomes, its high complication rate limits indications. Only Delalande's type I purely cisternal peduncular forms, when associated with drug-resistant epilepsy, remain a good indications to perform pterional approach[23,47]. Laser and radiofrequency coagulation procedures (Figure 4) are significant advances compared to the historical microsurgical procedures. Concerning the approaches making a lesion to the whole hypothalamic hamartoma, literature review suggests that multiple radiofrequency small lesions[37] have a better efficacy and safety than LiTT[20,34], probably due to the difficulty of the latter technique to target the whole lesion while sparing the adjacent structures (Figure 4). Nevertheless, these statement is based on single center results and will probably be counterbalanced by the recent advances of super-selective lesions performed with LiTT[82]. Disconnection approach by laser and radiofrequency coagulation in robot guided stereo-endoscopy provides very good results in term of seizure control and safety, probably due to possibility to fully disconnect the lesion and to spare the adjacent structures by a planar section (Figure 4)[25,26].

Going beyond the surgical technique, the analysis of the pathological functional connectivity of the hypothalamic hamartoma by resting state MRI made it possible to target a subpart of the lesion[6]. This approach coupled with LiTT procedures showed excellent results in term of seizure control and safety (Figure 4)[6]. These findings suggest that the true impact on the surgical results does not come from purely surgical technique (laser vs radiofrequency coagulation or stereotactic vs robot-guided stereo-endoscopy) but relies on the understanding of the epileptic network, including inside the epileptic hamartoma, that makes possible to plan a disconnection or a lesioning that spare the adjacent functional structures.

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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[51,67]	90%	55%	50%	30	Third nerve palsy Hemiplegia Diabetes insipidus Hyperphagia Memory impairment
Transcallosal approach[51,55,65]	90%	50-55%	10%	70	Memory impairment Thalamic infarction
Endoscopic resection[2,19,45,54]	80%	45-50%	8%	25	Memory impairment Hemiperesis
Stereotactic radiosurgery[16,47,60]	65%	25%	0%	80	-
LiTT (standard)[21,22,85]	80%	45%	25%	115	Memory impairment Hyperphagia
LiTT (fMRI targeted)[6]	90%	90%	0%	35	-
Stereotactic RF-TC[39]	80%	70%	2%	100	Diabetes insipidus
Endoscopic laser and RF-TC[28]	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.

Figure 1

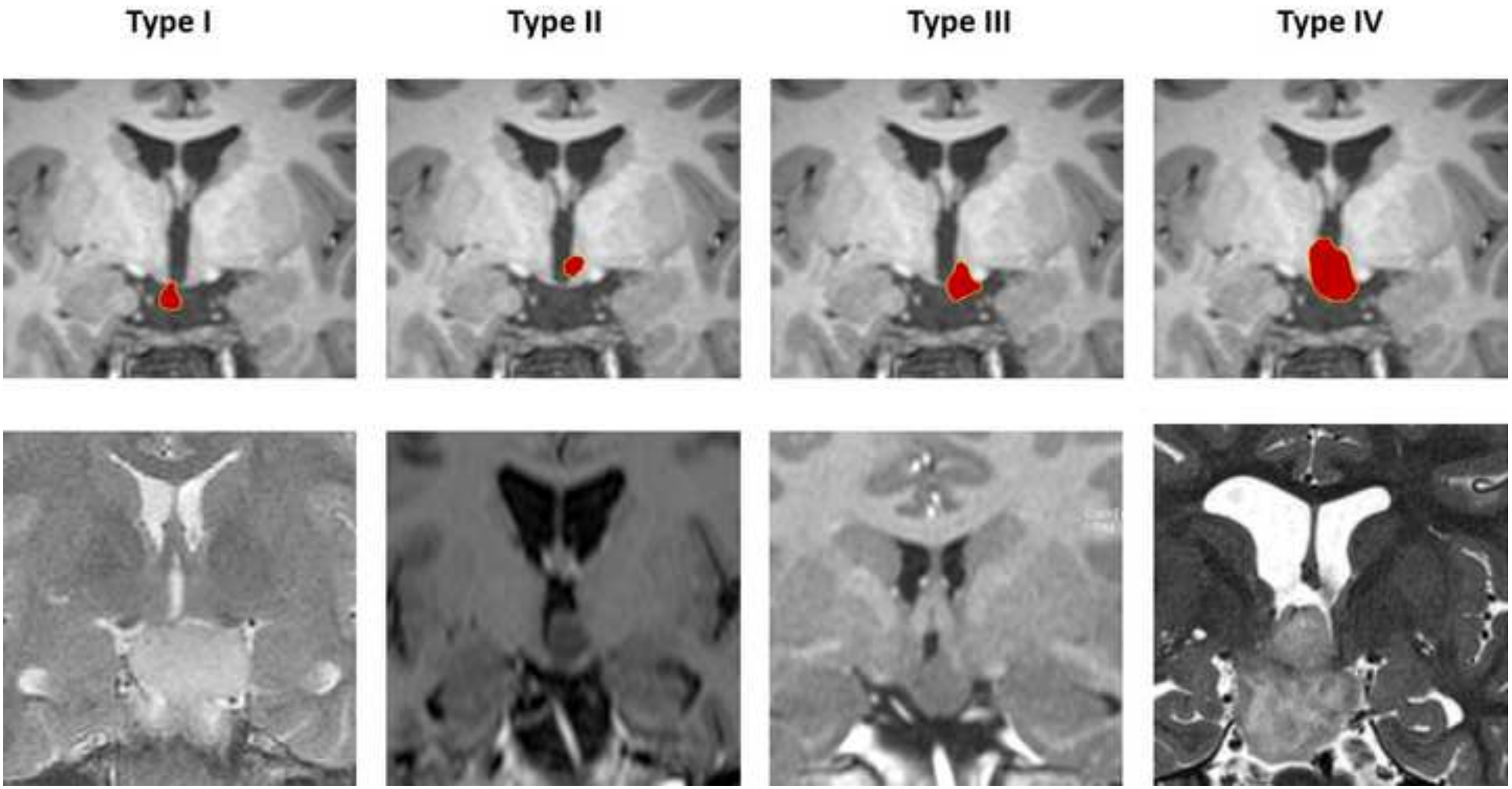
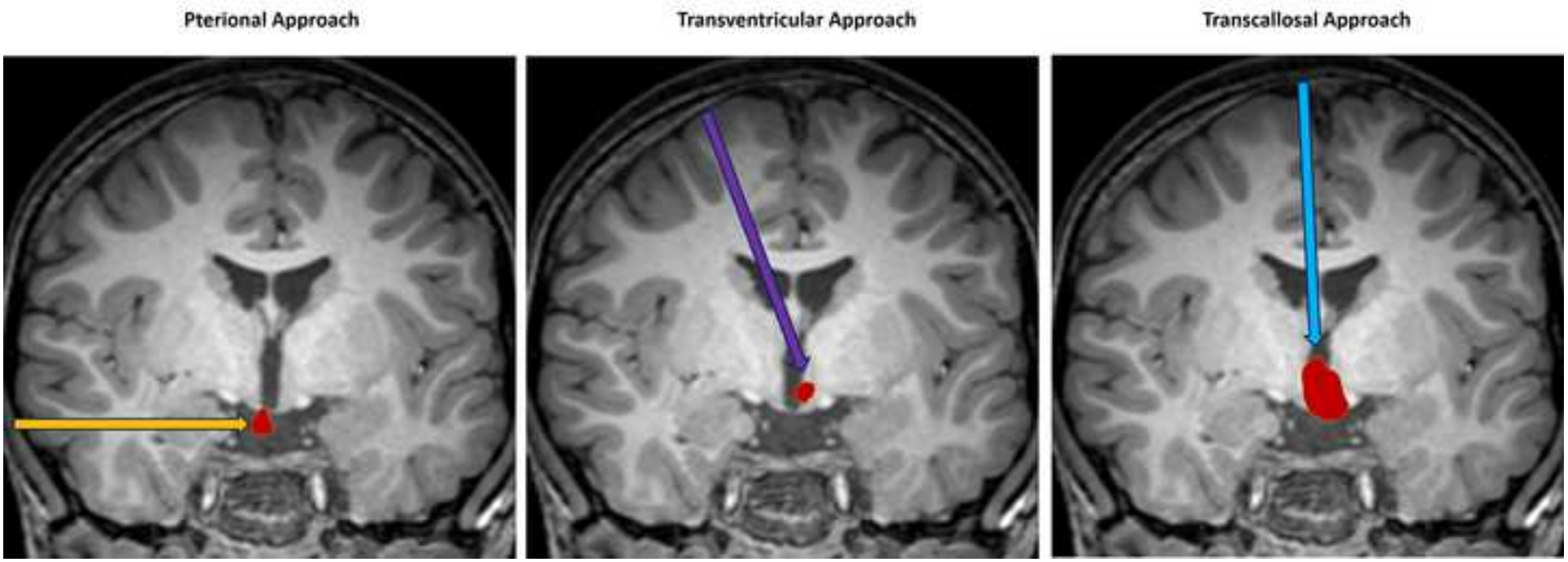


Figure 1.jpg

Figure 2



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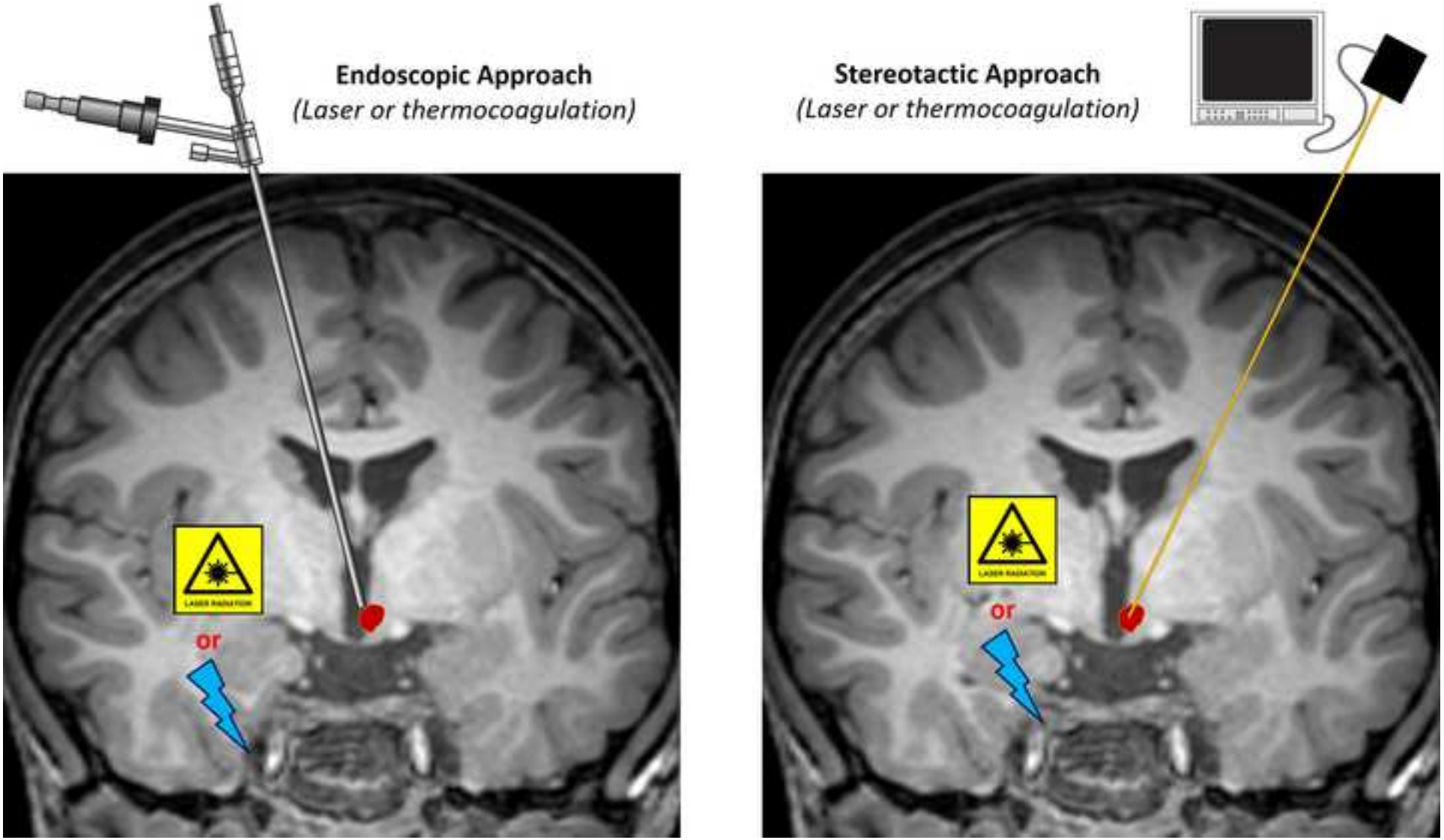
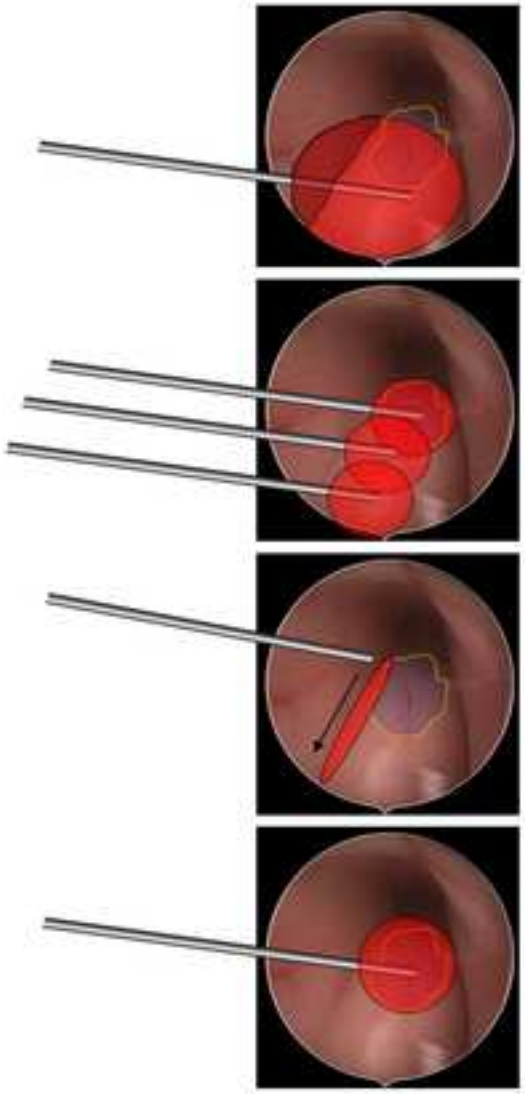


Figure 3.jpg



Single lesion (Laser - stereotactic)	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.	Xu & al. 2018 Curry & al. 2018 Hoppe & al. 2018
Multiple lesions (Radiofrequency coagulation - stereotactic)	Multiple stereotactic stereotactic lesions are preformed through multiple trajectories making easier to spare the adjacent structures bur requiring multiple electrode insertions.	Kameyama & al. 2016
Disconnection (Laser / Radiofrequency coagulation – robot guided stereo-endoscopy)	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.	Ferrand-Sorbet & al. 2020
Single lesion with epileptic zone targeting (Laser- stereotactic)	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.	Boerwinkle & al. 2018

Video 1

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Video 2

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