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## **Surgical techniques: Stereoelectroencephalography-guided radiofrequency-thermocoagulation (SEEG-guided RF-TC)**

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## **Abstract**

Stereoelectroencephalography-guided radiofrequency-thermocoagulation (SEEG-guided RF-TC) consists of coupling SEEG investigation with RF-TC stereotactic lesioning directly through the recording electrodes. In this systematic review the surgical technique, indications, and outcomes are described. Maximum accuracy is reached when a frame-based procedure with a robotic assistance and a per-operative vascular X-ray imaging are performed. Monitoring of the lesioning procedure based on the impedance, a sharp modification of which indicates that the thermocoagulation has reached its maximum volume, allows the optimization of the lesion size. The first indication concerns patients in whom a SEEG is required to determine whether surgery is feasible and in whom resection is indeed possible. Even if surgery is performed owing to insufficient efficacy of SEEG-guided RF-TC, the procedure remains interesting owing to its high positive predictive value for good outcome after surgery. The second indication concerns patients in whom phase I non-invasive investigations have concluded to surgical contraindication and who may still undergo SEEG in a purely therapeutic perspective (small deep zones inaccessible to surgery and network nodes of large epileptic networks). Lastly, SEEG-guided RF-TC can be considered as a first-line treatment for periventricular nodular heterotopia (PNH). Independently of indication, the overall seizure-free rate is 23% and the responder rate is 58%. The best results are obtained for PNH (38% seizure-free and 81% responders), while the worst results have been reported for temporal lobe-epilepsy in a dedicated study. The overall complication rate is 2.5%. More evidence is needed to help determine the exact place of SEEG-guided RF-TC in the surgical management algorithm.

## Introduction

Stereotactic neurosurgery was initially developed in the second half of the XX<sup>th</sup> century as a solution to the high morbidity of invasive open surgery[1]. Historically, in epilepsy surgery stereotactic procedures were mainly used to localize the seizure onset zones through the recording of intracranial-EEG by stereoelectroencephalography (SEEG)[2]. More recently, following the growing accuracy of the delineation of the seizure onset zone and epileptic networks, the surgical management of drug-resistant epileptic patients faced new challenges[3–5]. Alongside surgical advances in conventional epilepsy surgery, stereotactic lesioning has emerged as an alternative when surgery is not an option. Several stereotactic approaches have been developed, including radiosurgery[6], Laser Interstitial Thermotherapy (LiTT)[7–15], High Intensity Focal Ultrasound (HIFU)[16,17], and SEEG-guided Radiofrequency Thermo-Coagulation (SEEG-guided RF-TC)[18–27]. The present review focuses on the latter, which aims at coupling SEEG investigation with RF-TC stereotactic lesioning directly through the recording electrodes. This technique was first reported in 2004 in a feasibility study[18] with the initial aim to produce a lesion in the seizure onset zone, as an alternative to surgery. The subsequent publications highlighted the limits of this approach as a purely curative procedure and developed its use for palliative and diagnostic purposes[27–29]. More recently, the publication of several large series with long-term outcomes helped clarify the indications of SEEG-guided RF-TC. Nevertheless a meta-analysis recently highlighted the high heterogeneity of these studies[30].

Only one study has specifically focused on children[31], but large published series include a considerable pediatric population[22,32] and do not report significantly different results in such patients. Consequently, we chose to include all published studies investigating SEEG-guided RF-TC. For this, three electronic databases were searched (MEDLINE, Cochrane (CENTRAL) and the Web of Science) using the following search strategy: [Stereoelectroencephalography OR Stereo-electroencephalography OR SEEG] OR [Stereotactic AND (“Electroencephalography” OR “EEG”)] AND [Thermocoagulation OR TC OR radiofrequency OR RF OR radiofrequency-thermocoagulation OR RT-TC] OR [thermo-SEEG OR thermoSEEG] AND [Epilepsy OR Epileptic], limited to the period from January 1, 2004 to December 31, 2017. We will nonetheless provide additional insights about specific pediatric situations.

## **Surgical technique**

### *Materials*

All of the studies investigating SEEG-guided RF-TC were conducted using a radiofrequency lesion generator system Cosman G3 or G4 (Cosman Medical, Burlington, MA, USA) connected to the SEEG electrodes through a dedicated electrode selector. The most frequently used SEEG electrodes are the Microdeep electrodes (Dixi Medical, Besançon, France) which have a diameter of 0.8 mm, and include 5 to 18 recording contacts that are 2 mm in length and 1.5 mm apart[18,23]; Alcis SEEG electrodes (Alcis - Temis Santé, Besançon, France) are also approved for coagulation procedures.

### *Electrode placement*

As SEEG-guided RF-TC is an additional procedure performed during an SEEG, electrode placement technique of the latter procedure is crucial (see example in Figure 1). To be appropriate for RF-TC the electrode needs to reach the targeted anatomical structure with a good geometric accuracy in order to allow safe coagulations in rich vascular environments. These two aspects can be assessed through a common measure called the effective accuracy[33]. Very few studies provide comparison between SEEG techniques, but the use of a stereotactic-frame, a surgical robot, and a per-operative angiography (specifically compared to pre-operative angio-MRI) seems to be associated with a better effective accuracy[33,34]. Concerning the overall safety of electrode insertion, a meta-analysis recently found SEEG to be safe[35]. Evidence is still, however, lacking to clearly identify technical risk factors associated with poor safety as there are many biases that could hamper interpretation of results, but the best safety is obtained by teams performing a frame-based procedure coupled to a per-operative angiography or angio-CT[20,34–39].

### *Radiofrequency thermocoagulation*

The French national guidelines on SEEG include a section dedicated to SEEG-guided RF-TC and are, to date, the only recommendations published on this topic[40,41]. They slightly differ from the initial

description of the technique[18] as more recent laboratory investigations have found that two parameters determine the volume of the lesion: the dipole selection and the radiofrequency parameters[42,43].

The French guidelines recommend to create the dipole by selecting adjacent electrode contacts on a single electrode[40]. These contacts are conventionally located in cortical areas showing either a low amplitude fast pattern or spike-wave discharges at the onset of the seizures. Interictal paroxysmal activities can help to locate the ictal onset zone but when isolated are classically insufficient to be considered as a SEEG-guided RF-TC target[28]. Nevertheless, because of the high specificity of the spiking signature of type II focal cortical dysplasias[44], SEEG-guided RF-TC can be exceptionally performed where this signature is observed, even if no seizure has been recorded. Functionally evaluating all the possible targets by bipolar electrical stimulations (low and high frequency pulse stimulation up to 3mA) during the video-SEEG recording session is recommended to avoid side effects [40]. RF-TC may be reconsidered on dipoles whose stimulation provokes a neurological deficit. The direct electric stimulations for functional mapping are similar to those used for triggering seizures during the SEEG or when studying the functional connectivity within a network, and can be either low frequency shock or high frequency train stimulations. Train stimulations are particularly relevant for functional mapping of primary areas. The parameters for shock stimulations are 1 Hz frequency; a shock duration of 0.5 to 3 ms; an intensity of 0.5 to 4 mA (progressively increased); a stimulation duration of 20 to 60 s. The parameters for train stimulation are 50 Hz frequency; a shock duration of 0.5 to 1 ms; an intensity of 0.5 to 5 mA (progressively increased); a stimulation duration of 3 to 8 s[40].

Parameters of radiofrequency current can be adapted to optimize the size of the lesion. For each coagulation site, the maximal lesion volume may be reached by using parameters adjusted according to the impedance (which indicates when coagulation occurs), whereas the lesion size obtained using standard fixed parameters is usually smaller (see Figure 2)[45]. The power delivered (in practice, the voltage, since the intensity is automatically adapted by the radiofrequency generator) is therefore increased until the impedance suddenly increases (usually within a few seconds); *in vitro* data suggest that this is related to the coagulation of proteins producing a sudden modification of the resistance that

the tissue applies to the delivered sinusoidal current[45]. After this impedance change, any extra current delivered does not produce any increase of the size of the lesion.

## **Indications**

There is no high-level evidence concerning the indication of SEEG-guided RF-TC, and therefore the points presented in this section must not be interpreted as recommendations but as insight about frequent clinical situations and when to consider this procedure in the diagnostic/therapeutic algorithm.

The first historical indication of SEEG-guided RF-TC, which is still the most frequent one, concerns patients in whom a SEEG is needed to determine whether surgery is feasible and in whom resection finally appears to be indeed possible[28]. When the seizure onset zone is small enough to be entirely covered by the sum of the coagulation volumes, SEEG-guided RF-TC may be sufficient to cure the patient. In other cases, when only a portion of the seizure onset zone can be targeted by the RF-TC, the procedure remains a very helpful prognostic tool: the improvement of the epileptic status of the patient, even partial and time-limited, predicts with a high positive predictive value (93%) good outcome after conventional surgery [32]. It is worth mentioning that the negative predictive value is low; the absence of improvement of epilepsy after an SEEG-guided RF-TC does not therefore constitute an argument against surgical resection if the phase II investigations conclude to the presence of an accessible seizure onset zone. Very rarely, a partial lesion of a type II focal cortical dysplasia can lead to an increase of the seizure frequency – in which case rapid conventional surgery can be necessary if the adjustment of the drug regimen is insufficient to stabilize the situation. Concerning the very specific situation of temporal lobe epilepsy (TLE), for which LiTT is becoming increasingly popular as an alternative to amygdalo-hippocamnectomy, evidence indicates that SEEG-guided RF-TC is inferior to conventional surgery, and therefore SEEG must not be only justified by the possibility of performing stereotactic lesions in such cases[21].

More recently, some patients in whom phase I investigations concluded to a surgical contraindication underwent SEEG in a purely therapeutic perspective to perform SEEG-guided RF-TC. This situation can correspond to that of a small, but clearly inaccessible to resective surgery, suspected ictal onset zone requiring a SEEG confirmation. A good example would be an anterior insular focal cortical dysplasia covered by a language dominant operculum in a patient who cannot sustain awake surgery, or a periventricular nodular heterotopia sited along the tapetum [24,25]. Moreover, when the surgical contraindication found on phase I investigations is a large multi-lobar epileptic network, SEEG-guided RF-TC can be indicated as a palliative option. The goal is then to target crucial nodes within the epileptic network in order to limit the organization and the propagation of seizures[46]. Nevertheless, the definition of the network's nodes remains largely empirical (network modelling is not yet usable in clinical practice).

Concerning hypothalamic hamartomas, a preliminary study using SEEG-guided RF-TC has recently been published[47]. However, this type of lesional epilepsy exceptionally requires phase II investigations. Moreover, the good results obtained by surgery and radiosurgery[48], the better volume control of LiTT, and the difficulty to perform a meaningful functional mapping in this area makes it harder to justify SEEG-guided RF-TC in this condition. When economic constraints limit the access to the reference techniques, standard monopolar RF-TC remain an option[49].

The last very empirical and restricted indication is the use of SEEG-guided RF-TC as a diagnostic tool when multiple hypotheses are difficult to differentiate during a SEEG. In this specific case, the electrodes are left in place after the RF-TC and the SEEG continues. The analysis of the consequences of the lesions performed within the network can help to check the validity of the different hypotheses.

## **Outcome**

A recent meta-analysis that included 6 studies[19,22,24,26,27,32] and a total of 296 patients found a seizure-free rate of 23% and a responder rate of 58% one year after the SEEG-guided RF-TC, responders being defined as those with 50% or greater reduction in seizure frequency as compared to the pre-



procedure period[30]. At the study level, meta-regression failed to identify factors impacting the seizure-free rate, including the number of RF-TC. Furthermore, therapeutic efficacy was very heterogeneous, limiting the interpretation of the pooled result. It also remained high in sub-group analyses which indicates that heterogeneity was not only related to variable efficacy with regards to the underlying lesion and that it could, in part, be related to variations in the management of SEEG-guided RF-TC across centers.

It is worth mentioning two specific etiologies in which the results differ from the general results and must lead to specific indications or contraindications. On the one hand, results of SEEG-guided RF-TC in periventricular nodular heterotopias are particularly interesting: among such patients treated with SEEG-guided RF-TC it has been reported that 38% were seizure free and 83% were responders [30]. On the other hand, in TLE a controlled study found that SEEG-guided RF-TC was inferior to anterior-temporal lobectomy (ATL); none of the patients who underwent SEEG-guided RF-TC was seizure-free at one year (versus 75% in the ATL group), and only 48% percent were responders (versus 100% in the ATL group)[21]. No other published study has focused specifically on other etiologies and sub-group analysis has failed to identify other etiologies as having good or bad prognosis[30].

Emergence of SEEG-guided RF-TC has led to extend indications of SEEG for patients who are not eligible for conventional surgery. The implantation strategies may sometimes have also deeply evolved, for instance in over implanting a suspected well-limited seizure onset zone in order to perform a curative RF-TC procedure or to target network nodes for patients in whom only a palliative approach may be considered. Nevertheless these modifications of SEEG implantation strategies are very difficult to assess and none of the published studies investigating SEEG-guided RF-TC provide an evaluation of this. Concerning safety, the previously mentioned meta-analysis found homogeneous results across studies. The pooled complication rate of SEEG-guided RF-TC was 2.5% and, among those reported, only one (0.3%) was a non-expected deficit with minimal consequences on the patient's daily life (hypoesthesia of the right thumb)[30]. The other complications were neurological deficits that were anticipated during the pre-procedure functional mapping by direct electric stimulation and corresponding to a very well circumscribed seizure onset zone situated in the primary motor area. The RF-TC was thus carefully

discussed with the patients who were aware that the deficit noticed during functional mapping would occur after the lesion and may permanently remain[30].

## **Conclusion**

The increasing number of studies investigating SEEG-guided RF-TC have established that this surgical procedure is remarkably safe. More evidence is necessary to determine the exact place of SEEG-guided RF-TC in the surgical management of drug-resistant epilepsies, but two situations emerge in which SEEG-guided RF-TC may be considered in clinical practice. First, in patients requiring a SEEG in their presurgical evaluation, and when SEEG succeeds in delineating an accessible seizure onset zone, SEEG-guided RF-TC should be considered; although the probability of avoiding surgery by curing the patient is low the positive predictive value of a possible effect, even partial, of the RF-TC is valuable in the decision to proceed or not with surgery. Secondly, when the suspected seizure onset zone is not surgically accessible, but limited in size, a SEEG could be justified for the purpose of performing a SEEG-guided RF-TC, even if surgical resection is not an option. A good illustration of this indication is periventricular nodular heterotopias; these are rarely accessible to surgery and require SEEG to determine the respective contribution of the heterotopia and neocortex in the epileptic network. Subsequent SEEG-guided RF-TC allows a one-step procedure providing very encouraging results and might therefore be considered as an effective first-line treatment for periventricular nodular heterotopias-related drug-resistant epilepsy, LiTT being an interesting alternative option. Concerning TLE, SEEG-guided RF-TC is inferior to the gold standard technique and should not be used as an alternative.

## **Disclosure**

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure 1: Procedure workflow.

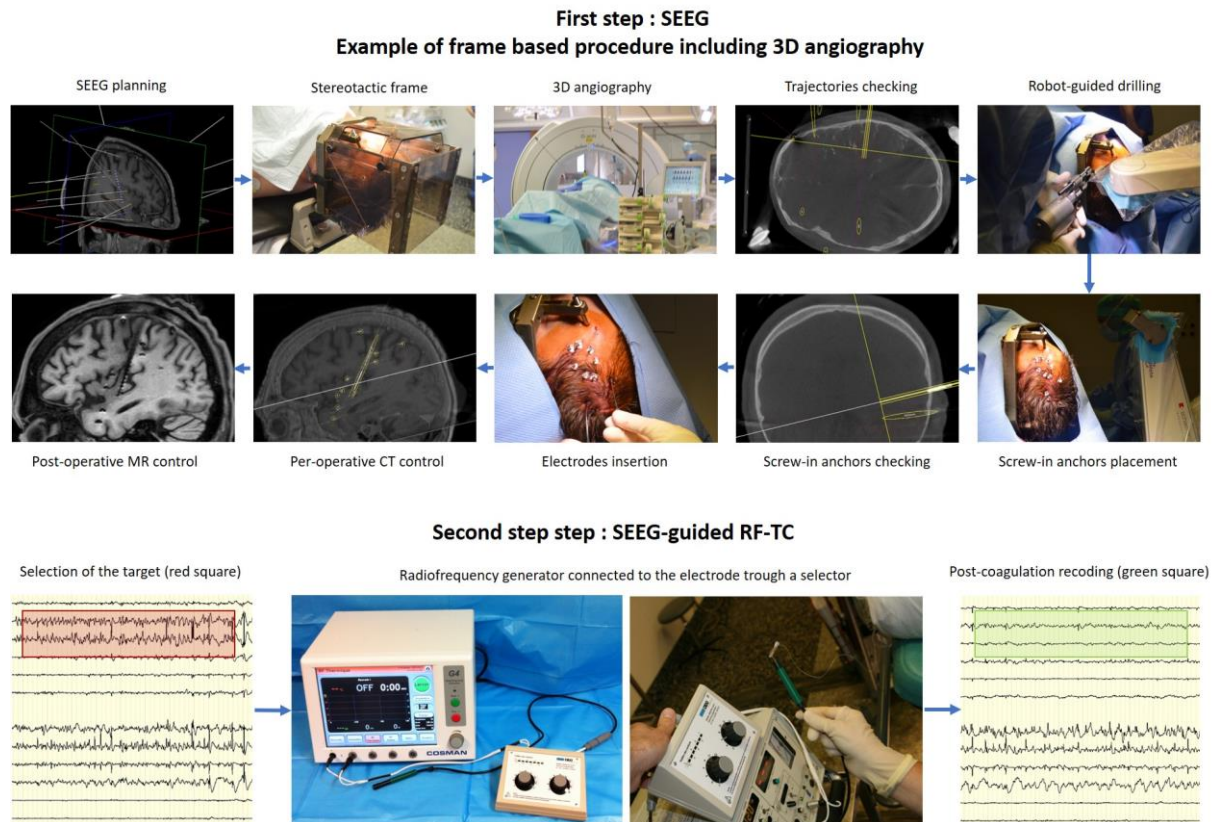


Figure 2: a. *in vitro* aspect of multiple thermocoagulation on a single electrode; b. MRI aspect of multiple thermocoagulation on a multiple electrodes (red arrows).

