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REVIEW

Seizure outcomes in nonresective epilepsy surgery: an update

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Abstract In approximately 30 % of patients with epilepsy, seizures are refractory to medical therapy, leading to significant morbidity and increased mortality. Substantial evidence has demonstrated the benefit of surgical resection in patients with drug-resistant focal epilepsy, and in the present journal, we recently reviewed seizure outcomes in resective epilepsy surgery. However, not all patients are candidates for or amenable to open surgical resection for epilepsy. Fortunately, several nonresective surgical options are now available at various epilepsy centers, including novel therapies which have been pioneered in recent years. Ablative procedures such as stereotactic laser ablation and stereotactic radiosurgery offer minimally invasive alternatives to open surgery with relatively favorable seizure outcomes, particularly in patients with mesial temporal lobe epilepsy. For certain individuals who are not candidates for ablation or resection, palliative neuromodulation procedures such as vagus nerve stimulation, deep brain stimulation, or responsive neurostimulation may result in a significant decrease in seizure frequency and improved quality of life. Finally, disconnection procedures such as multiple subpial transections and corpus callosotomy continue to play a role in select patients with an eloquent epileptogenic zone or intractable atonic seizures, respectively. Overall, open surgical resection remains the gold standard treatment for drug-resistant epilepsy, although it is significantly underutilized. While nonresective epilepsy procedures have not replaced the need for resection, there is hope that these additional surgical options will increase the number of patients who receive treatment for this devastating disorder—particularly individuals who are not candidates for or who have failed resection.

Keywords Brain stimulation · Disconnection · Epilepsy surgery · Review · Seizure outcome

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Introduction

Uncontrolled seizures lead to significant morbidity and increased mortality, but patients with drug-resistant epilepsy may be candidates for epilepsy surgery [22, 35]. Established guidelines recommend that patients with epilepsy who have failed two or more antiepileptic drug trials are unlikely to achieve seizure freedom with further medication changes alone, and should thus be referred to a comprehensive epilepsy center for surgical evaluation [24, 35, 82]. In mesial temporal lobe epilepsy (MTLE) and focal neocortical epilepsy (FNE), localization and resection of the epileptogenic zone (EZ) is the gold standard surgical treatment in both children and adults [40, 44, 49, 51, 116], and the use of anterior temporal lobectomy for drug-resistant MTLE is supported by two randomized controlled trials [34, 130]. In the present journal, we recently provided an update of rates and predictors of seizure freedom with resective epilepsy surgery across recent literature [41]. However, not every patient with drug-resistant epilepsy is a candidate for or amenable to surgical resection, so a thorough understanding of nonresective surgical alternatives is imperative in the treatment of this disorder. Thus, the goal of the present review is a concise yet comprehensive summary of seizure outcomes after nonresective surgical procedures for epilepsy, including a critical overview of recent important literature. While most studies investigate patients

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who have not received prior open surgical resection for epilepsy, we also reference manuscripts examining outcomes of nonresective surgery after failed resection, given that reoperation represents another aspect of surgical care [37].

While the goal of epilepsy resection is to excise abnormal region(s) of the brain harboring an EZ in hopes of achieving seizure freedom, patients with generalized epilepsy syndromes or seizure foci that are poorly localized, multifocal, or positioned in eloquent brain regions are often not candidates for resection [16, 41]. For these individuals, palliative surgical options may be considered to reduce the frequency and severity of seizures, and these include stimulation-based therapy using vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS), as well as disconnection procedures such as multiple subpial transections (MST) and corpus callosotomy (CC). Unlike disconnective surgeries, each of the three stimulation treatment strategies has been evaluated in randomized, controlled trials. Furthermore, novel techniques for EZ ablation, such as stereotactic laser ablation (SLA) and stereotactic radiosurgery (SRS), now allow minimally invasive surgical options for select individuals who are poor candidates for open surgery, or are simply averse to it. Importantly, reporting of outcome measures in the literature often differs somewhat between interventions. As with resection, the ultimate goal of ablation is typically complete seizure freedom, and thus seizure freedom rates are the primary outcome measure reported for ablative interventions. However, complete seizure freedom is rare after palliative neurostimulation, and therefore, percent decrease in seizure frequency and rate of response to therapy (defined as ≥50 % decrease in seizures) are typically reported as primary outcome measures for these procedures. Finally, callosotomy studies usually report reduced frequency of drop attacks.

Ablative procedures

The primary objective of ablative procedures for intractable focal epilepsy resembles the goal of resective strategies: destruction of epileptogenic tissue to prevent further seizures. Two ablative therapies for epilepsy pioneered in recent years, SLA and SRS, lead to tissue necrosis using thermal energy or radiation, respectively. In general, these procedures offer a minimally invasive alternative to craniotomy for patients with significant risk factors for open surgery.

Stereotactic laser ablation

Radiofrequency thermoablation has been used for focal stereotactic brain lesioning in the treatment of intractable epilepsy. In one series of 22 patients with MTLE, stereotactic radiofrequency amygdalohippocampectomy resulted in complete seizure freedom in two (9 %) patients, and worthwhile improvement was observed in an additional eight (25 %) individuals [97]. Case reports examining the use of radiofrequency ablation for hypothalamic hamartomas have revealed favorable seizure outcomes in some patients, and three of five (60 %) individuals treated achieved seizure freedom in one small case series [75]. Radiofrequency ablation has also been reported in patients implanted with diagnostic stereotactic depth electrodes, utilizing recording electrodes to lesion a confirmed epileptogenic region [62, 63]. Finally, radiofrequency ablation for periventricular heterotopia has also been described with some success [112]. However, given improvements in MRI thermometry, and challenges related to monitoring and controlling radiofrequency lesions, interest in real-time stereotactic ablation using laser thermal energy has recently increased [61, 118].

The SLA procedure can be performed with a small scalp incision and miniature burr hole, with a laser probe placed using a stereotactic frame or interventional MRI techniques. The most interest in SLA for epilepsy has been focused on selective lesioning of the amygdalohippocampal complex in MTLE [70, 127, 133]. Approaching the hippocampus from an occipital trajectory along its longitudinal axis allows access to a large portion of the structure, while the inferior horn of the lateral ventricle (laterally) and the basal cisterns (medially) create a "heat sink" that helps prevent thermal injury to nearby structures and vasculature [60, 134]. MRI images from an example case of SLA for MTLE are shown in Fig. 1.

Willie and colleagues reported a series of 13 adult patients who received SLA for MTLE with or without mesial temporal sclerosis [133]. The authors reported a mean volume of 60 % ablation of the amygdalohippocampal complex and a median hospitalization of only 1 day. After 5 to 26 months of follow-up, with a median of 14 months, 54 % of patients were free of disabling seizures, and 67 % (6 of 9) of individuals with mesial temporal sclerosis were seizure free. Seizure recurrences were all observed within the first 6 months, and differences in ablation volume or length did not account for clinical outcomes. There was one significant adverse event involving a visual field defect caused by deviated insertion of a stereotactic aligning rod, although the alignment was corrected prior to ablation [133]. A follow-up study by the same group examined certain neuropsychological outcomes in 19 patients undergoing SLA for MTLE, compared to 39 individuals undergoing standard resection, using a prospective, nonrandomized, parallel-group design [31]. Compared to open surgical resection, it was found that SLA was associated with significantly improved naming in patients with dominant hemisphere MTLE and better object recognition in individuals with MTLE of the nondominant hemisphere. Overall, no patients showed decline in performance in naming and object recognition tasks after SLA, suggesting that the hippocampus does not play an essential role in these neural networks [31]. Another group examined SLA outcomes in 20 patients with MTLE and measured ablation

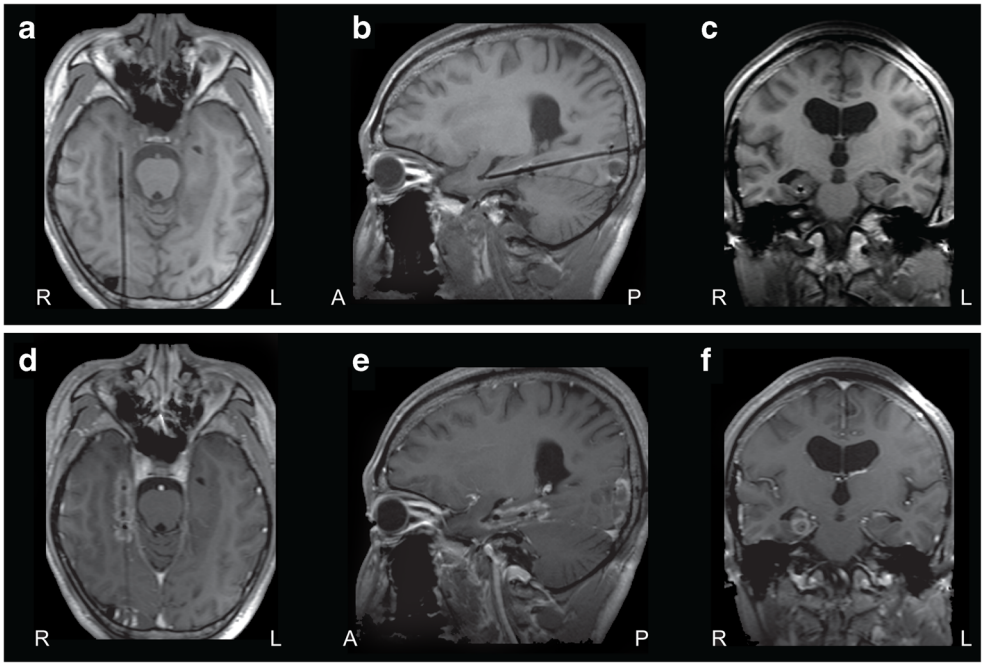

Fig. 1 Stereotactic laser ablation (SLA) for mesial temporal lobe epilepsy. **a**–**c** Shown are T1-weighted MRI axial (**a**), sagittal (**b**), and coronal (**c**) images showing during laser probe placement along the axis of the left hippocampus, prior to SLA in a patient with mesial temporal lobe epilepsy. **d**–**f** Contrast-enhanced T1-weighted MRI axial (**d**), sagittal (**e**), and coronal (**f**) images obtained approximately 5–10 min after thermal ablation of mesial temporal lobe structures, with contrast enhancement seen in the region of ablation. Lesioning is performed with real-time MRI thermal measurements. *A* anterior, *L* left, *P* posterior, *R* right

volumes [77]. Seizure freedom was reported in 53 % of 15 patients at 6 months, 36 % of 11 patients at 1 year, and 60 % of 5 individuals at 2 years (median follow-up, 13 months). No differences were noted in total ablated volumes of hippocampus, amygdala, parahippocampal gyrus, entorhinal cortex, and fusiform gyrus in patients who did or did not achieve seizure freedom.

SLA outcomes have also been examined in pediatric patients with various epilepsy etiologies [15]. In a recent series of 19 pediatric patients receiving SLA for intractable epilepsy, Lewis et al. reported seizure freedom in 41 % of individuals after a mean follow-up of 16 months (range 4 to 36) [84]. Nearly all of these patients suffered from FNE, with epilepsy etiology in 11 individuals consistent with focal cortical dysplasia, and 10 patients had received prior resection. Thus, as with resective surgery, seizure outcomes with SLA for FNE appear inferior to outcomes in the treatment of MTLE.

Another study reported the use of SLA to treat cavernous malformations associated with drug-resistant epilepsy in five patients, observing seizure freedom in four (80 %) individuals 12 to 28 months after treatment [89]. Furthermore, some groups have successfully used SLA to treat hypothalamic hamartomas associated with epilepsy—a lesion that is particularly challenging to access safely with open surgery [131]. These reports suggest that SLA may be a feasible treatment alternative to resection with other epileptogenic lesions beyond mesial temporal lobe structures.

Overall, early patient series suggest relatively favorable outcomes with SLA for patients with focal epilepsy—particularly those with MTLE—although seizure freedom rates are lower than those with traditional resection. Nonetheless, the minimally invasive nature of this procedure may make it a desirable treatment option for patients who are averse to resection, or those with significant surgical risk factors. Further studies are needed to define long-term seizure and neuropsychological outcomes after SLA and to better elucidate the role and efficacy of surgical resection in patients who have failed ablation as an initial operative therapy. Furthermore, no previously published SLA studies have specifically examined patients who failed prior epilepsy surgery, but such investigations will be important going forward.

Stereotactic radiosurgery

SRS for MTLE is the only nonresective procedure for epilepsy which completely avoids invasive surgery. SRS is performed with gamma knife-targeted radiation, which uses radioactive cobalt to deliver 192 beams of radiation to a targeted area of the brain in a single fraction while preserving surrounding parenchyma [59, 102, 103]. Similar to SLA, SRS may be a favorable option for patients with MTLE who refuse resection or have medical comorbidities that increase perioperative risk. Early studies have examined the safety and efficacy of SRS for MTLE patients with mesial temporal sclerosis [7, 103, 104]. In general, seizure outcomes in these reports have been relatively comparable to open temporal lobectomy, particularly in patients receiving high-dose therapy (24 Gy) to the amygdala, hippocampal head, and parahippocampal gyrus.

Barbaro et al. reported a pilot multicentered prospective trial of SRS for MTLE and observed seizure freedom in 77 % of 13 patients who received high-dose (24 Gy) treatment

and in 59 % of 17 individuals who received low-dose (20 Gy) therapy 1 year after the procedure [7]. This data suggests statistically improved efficacy of high-dose compared to low-dose SRS for MTLE. Among these patients, verbal memory impairment was noted in 15 % of patients, although none declined on more than one measure, while verbal memory improvement was seen 12 % of individuals [7, 101]. Side effects were minimal and included transient steroid requirements, headache, and visual field deficits. One individual suffered from malignant edema after treatment, including severe headaches, visual field deficit, and papilledema not responsive to steroids, and this patient eventually required temporal lobectomy [7]. The final results are awaited from a prospective randomized trial of SRS versus open temporal lobectomy (Radiosurgery or Open Surgery for Epilepsy [ROSE] trial) [107]. Of note, while most SRS epilepsy studies examine patients who have not undergone prior intervention, one small series reported SRS outcomes in four patients who failed open temporal lobectomy [137]. With a follow-up of 19–24 months, these patients had a 42 % mean decrease in seizure frequency (range 28–67 %) after SRS, but no patients were completely free of seizures.

Importantly, unlike resection, the beneficial effects of SRS on seizures in MTLE are typically delayed up to 12 months or more after treatment. Chang and colleagues found that MRI characteristics during the first year following SRS may serve as a predictor of seizure outcome at 3 years after therapy [18]. Specifically, T2 hyperintensity volumes 9 months after the procedure were found to be highly related to seizure remission and were more pronounced in patients who received 24 Gy SRS compared to lower dose 20 Gy treatment [7, 17]. Spectroscopy suggested a mechanism of action consistent with radiation necrosis, revealing that the treatment indeed results in tissue destruction. The development of these radiographic changes over time after SRS are summarized in Fig. 2. Thus, compared to SLA, which results in immediate tissue necrosis from thermal damage (e.g., Fig. 1), SRS results in delayed radiation necrosis. Similarly, the clinical benefits of SRS on seizure status are also delayed, compared to the immediate clinical effects observed after SLA. Future investigations will need to evaluate long-term seizure and cognitive outcomes in SRS compared to resection and SLA.

Neurostimulation procedures

While seizure freedom is usually the goal of resective and ablative procedures for epilepsy, device implantation for neurostimulation in epilepsy typically represents a palliative treatment approach. Complete seizure freedom is uncommon with current neuromodulation technologies, and thus reduction of seizure frequency and morbidity and improvement in quality of life are the primary treatment goals. The three neurostimulation options for epilepsy which have been well-studied include VNS, DBS, and RNS.

Vagus nerve stimulation

Approved by the United States Food and Drug Administration (US FDA) in 1997 and adopted in more than 70 countries, VNS is utilized for localization-related epilepsy with multiple or nonresectable foci, after unsuccessful intracranial epilepsy operations, and in generalized epilepsy syndromes [27, 53]. The primary delivery mechanism of VNS is a neurocybernetic prosthesis, and animal and human studies suggest that vagal stimulation may lead to desynchronization and decreased abnormal spike activity on EEG by enabling nonselective and bidirectional activation of nerve fibers [19, 74, 79]. Currently, over 100,000 VNS devices have been implanted worldwide [27].

Three blinded, randomized controlled trials have shed light on VNS efficacy for medically refractory epilepsy. First, Ben-Menachem and colleagues performed a randomized study with 114 focal epilepsy patients who received either therapeutic or sham stimulation after VNS implantation. They reported a significantly greater reduction in seizure frequency with therapeutic stimulation after 3 months of treatment (25 versus 6 %) [10]. Handforth and colleagues also led a multicentered trial of 196 patients with partial epilepsy and observed a 28 % reduction in seizure frequency with high stimulation versus 15 % with sham stimulation [67]. Overall, 23 % of individuals in the therapeutic group reached ≥50 % seizure reduction at 3 months. Next, Amar et al. observed more dramatic results in a small VNS trial including 17 patients, within which 57 % of individuals receiving therapeutic stimulation achieved ≥50 % decrease in seizure frequency [3]. Two nonblinded, randomized trials have also reported significant decreases in seizure frequency with various VNS stimulation paradigms [28, 110].

Although these randomized controlled trials of VNS included only a short follow-up period, observational studies have demonstrated improved efficacy over time with treatment. One large meta-analysis of patients treated with VNS included 3321 patients from 77 reports. Reduction in seizure frequency as compared to the baseline indicated that 51 % of patients treated with VNS obtained ≥50 % seizure frequency [43]. Seizure control rates rose as therapy duration increased, although few patients achieved complete seizure freedom. Similar outcomes were observed through unblinded analysis of the device manufacturer's patient database [42]. Favorable response to therapy, with ≥50 % reduction in seizure frequency, was reached by 1972 of 4483 (44 %) patients after 3 months of therapy and by 618 of 1104 (56 %) patients after 24 months. Patients with a history of Lennox-Gastaut syndrome or epilepsy stemming from a traumatic source may benefit from an improved treatment response [50]. Adverse events associated with VNS include hoarseness (37–62 %),

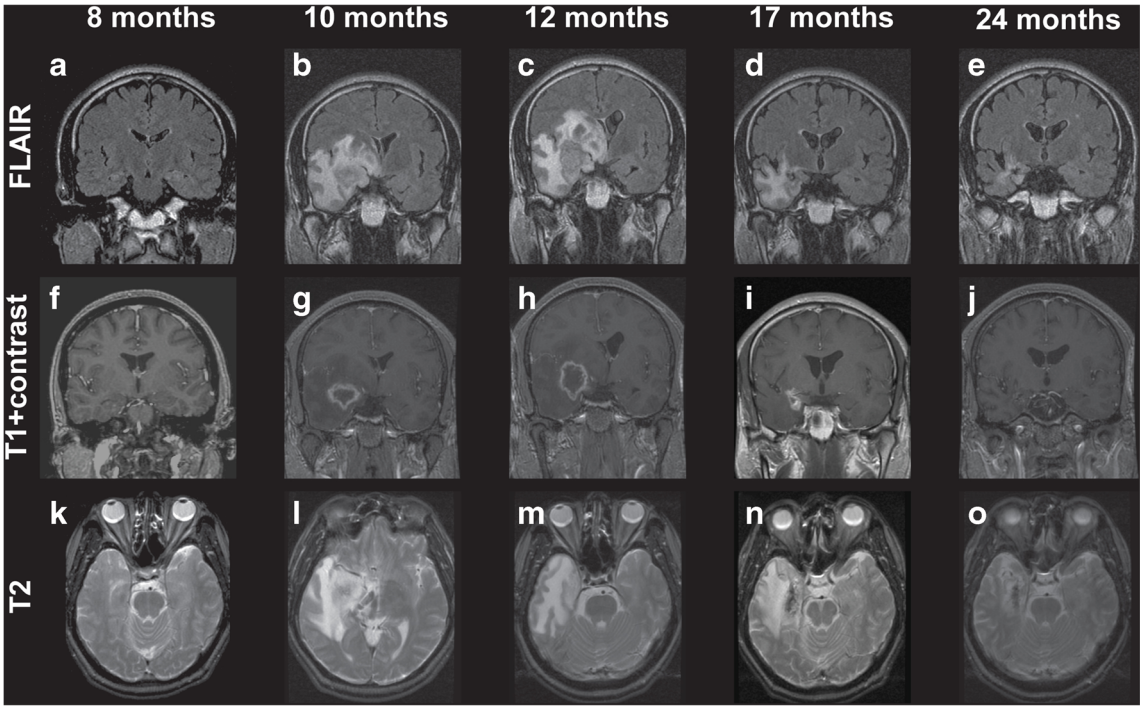

Fig. 2 Development of radiologic changes in a patient with mesial temporal lobe epilepsy treated with a 24-Gy dose gamma knife stereotactic radiosurgery (SRS). FLAIR (**a**–**e**) and T2 (**k**–**o**) hyperintensity appeared within the medial temporal lobe beginning by the 10th postoperative month and peaked in intensity at 12 months, corresponding to a decline in the proportion of patients experiencing complex partial seizures. Contrast enhancement (**f**–**j**) followed a similar time course, except that it preceded T2 changes and diminished quickly after months 10–12. Enhancement was typically ring enhancing and centered over the target region. Figure and legend reproduced with license and permission from Chang et al. [17]

cough (7–21 %), pain (6–17 %), and infection (4–6 %) [10, 29, 42, 67]. A Cochrane systematic review of VNS efficacy and tolerability for partial seizures among 439 patients was also recently conducted. The four trials analyzing high-level stimulation compared to low-level stimulation were summarized and together revealed an overall risk ratio of 1.73 for 50 % or greater seizure reduction [96].

One study of the VNS Therapy Patient Outcome Registry compared seizure outcomes after VNS in 921 patients who failed prior resection, compared to 3822 individuals who did not have previous surgery [2]. The median reduction in seizure frequency at 24 months was lower in patients who had failed previous surgery (51 %) compared to those who had not (67 %) undergone prior resection. A responder rate of 55 versus 62 % was seen in these two groups, respectively, at last follow-up. These data suggest that individuals who have failed epilepsy surgery may have less favorable VNS outcomes than patients without a history of resection, but may nonetheless experience worthwhile improvement in seizure frequency.

Finally, while complete seizure freedom is relatively rare with VNS, seizure freedom rates and predictors were recently examined across 5554 patients in the VNS Therapy Patient Outcome Registry and in a systematic literature review of 78 studies including 2869 patients [52]. Overall, seizure freedom rates ranged from 3 % after 0 to 4 months of treatment to 8 % after more than 2 years of therapy. Predictors of seizure freedom included age of epilepsy onset of greater than 12 years and a predominantly generalized seizure type [52]. Overall, when resective epilepsy surgery is not a viable treatment option, or in individuals who have failed open surgery, VNS may represent worthwhile palliative therapy for pharmacoresistant epilepsy. However, patients and providers must recognize that substantial clinical benefit (>50 % decrease in seizures) is only experienced in 50–60 % of patients who receive VNS and maximum seizure reduction may require 1–2 years of stimulation.

Deep brain stimulation

In the mid-twentieth century, the cerebellum was identified as a potential stimulation target for intractable epilepsy, thought to cause thalamic inhibition by increasing Purkinje cell output, but the degree of benefit was unclear due to nonblinded studies with unquantified outcomes [23, 93]. Hippocampal DBS has also been proposed in the treatment of epilepsy, in part given the effects of stimulation on desynchronization of mesial temporal networks [122]. Animal models of hippocampal DBS for epilepsy have demonstrated moderate efficacy [66]. In a kainic acid macaque primate epilepsy model, hippocampal stimulation has been shown to be protective again

neuronal apoptosis [20], and high-frequency stimulation of the hippocampus in kindled rats has been associated with higher threshold and longer latency of afterdischarges [135]. Nevertheless, a randomized controlled trial of hippocampal DBS in humans has not yet been reported [66, 120].

The subthalamic nucleus is a common DBS target for Parkinson's disease, and some investigators have examined subthalamic stimulation for epilepsy, hypothesizing that basal ganglia modulation may impact epileptogenicity [83]. Specifically, a few reports have found decreased seizure frequency in a small number patients with myoclonic epilepsy, but a large-scale investigation has never been pursued with this target [126, 132]. Given its role in cortical activation, DBS of the centromedian nucleus of the thalamus has also been explored in refractory epilepsy. Velasco and colleagues reported reduced rates of generalized seizures and improved quality of life in 13 patients with Lennox-Gastaut syndrome [125]. Another group evaluated centromedian nucleus stimulation versus sham treatment in six patients with intractable seizures and observed a 30 % decrease in seizures with stimulation, although this difference was not significant [56]. These and preliminary results from other groups [4, 123] suggest that the centromedian nucleus may be a target worthy of further study. Finally, beyond decreasing seizure frequency, rodent studies have suggested that thalamic stimulation may prevent aberrant network effects of seizures that lead to ictal impairment of consciousness [65], perhaps by effecting networks involved in normal cortical activation [45, 46]. However, human studies examining ictal effects of thalamic stimulation have not yet been performed.

In DBS for epilepsy, recent focus has turned to the anterior nucleus of the thalamus, a structure in the classic circuit of Papez intimately connected to limbic structures and with widespread neocortical projections [57, 106]. Thalamic DBS has been approved as adjunctive treatment for medication-resistant epilepsy as well as secondary generalized seizures in Canada, the European Union, Australia, Taiwan, New Zealand, and Australia, but it is not yet approved by the US FDA [8, 53]. While the mechanisms underlying DBS in general remain unknown, many have suggested that high-frequency stimulation (>50 Hz) produces a reversible lesion that mimics ablation [83].

Thalamic DBS was studied in 110 adults with medication-resistant partial epilepsy with or without secondary generalization in the randomized Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial [54]. During the 3-month blinded period of the SANTE trial, individuals receiving stimulation showed a significantly greater decrease in seizure frequency (40 %) compared to those in the control arm of the study (15 %). During the unblinded phase of the study, within which all patients were treated with stimulation for 2 years, seizure frequency was reduced by 56 % (median), and 54 % of patients experienced a reduction in seizure frequency of ≥50 %. A trend was observed toward improved seizure control with longer stimulation periods, as has been seen with other neurostimulation treatments such as VNS [42]. Recently, long-term outcomes have been reported by the SANTE investigators, revealing a median percent seizure reduction of 69 % and responder rate of 68 % 5 years after surgery [109]. This suggests that a beneficial neuromodulatory effect of DBS may extend beyond the first few years of therapy.

During the first year of thalamic DBS, adverse events include paresthesias in 18 % of individuals, surgical site pain in 11 %, local infections in 9 %, and need for lead replacement in 8 %, although these complication rates decreased in the second treatment year [54]. The overall rate of serious side effects secondary to the treatment was l–2 %. Neuropsychological testing revealed no differences in mood or cognitive between treated and untreated patients, but individuals receiving stimulation were more likely to report symptoms of depression. Given that rates of seizure control after thalamic DBS years versus VNS are relatively similar 1 to 2 years after implantation, a detailed comparative investigation of palliative neurostimulation procedures among patient subpopulations will likely be informative. Furthermore, DBS outcomes in epilepsy patients who have failed epilepsy resection will be an interesting topic for future exploration, given the absence of literature on this topic.

Responsive neurostimulation

While VNS and DBS use open-loop stimulation paradigms with uninterrupted electrical pulses, RNS utilizes a closed-loop stimulation system [106]. Implanted subdural and depth electrodes continuously record neurophysiological signals during ictal events, and these data can be analyzed offline for programming of the device. Then, stimulation is triggered by electrographic activity for seizure initiation, designed to terminate the epileptic discharge before it becomes symptomatic [92]. The RNS device, which is depicted in Fig. 3, received approval by US FDA in 2013 for the treatment of adults with intractable partial epilepsy [53]. While VNS and DBS do not require a hypothesis regarding EZ localization and indeed may be used in generalized epilepsy syndromes, RNS does require knowledge regarding seizure localization in order to effectively deliver targeted therapy. With current technology, up to two regions can be simultaneously targeted for active therapy with RNS. Thus, RNS is typically pursued in patients with multiple EZs—such as bilateral mesial temporal seizure onset—or an EZ located in eloquent cortex not amenable to resection [16, 78].

The efficacy of RNS was first examined in a multicentered, randomized, double-blinded, controlled trial termed the RNS System Pivotal Trial [92]. In this trial, 191 adult patients with drug-resistant partial epilepsy received implantation of the RNS system and were randomized to receive responsive stimulation versus seizure detection without stimulation during a

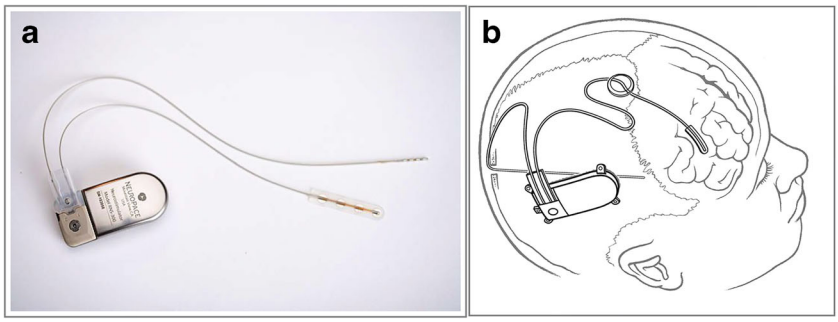

Fig. 3 The responsive neurostimulation device (RNS). **a** Shown is a NeuroPace RNS device configured for stimulation of one four-contact depth electrode and one four-contact strip electrode. **b** Artistic depiction of implanted RNS device, including a depth electrode and a cortical strip electrode. Images provided courtesy of NeuroPace

12-week blinded period. Individuals receiving stimulation experienced a reduction in seizure frequency of 38 versus 17 % in the sham treatment group. Also, 29 % patients receiving stimulation reported ≥50 % reduction in seizures, while this outcome was reported in 27 % of control subjects. After 3 months of randomization, individuals in both groups then received therapeutic stimulation. In this open study phase, 44 or 55 % of individuals experienced ≥50 % reduction in seizure frequency at 1 or 2 years, respectively. Furthermore, the median percent seizure reduction was 44 % at 1 year and 53 % at 2 years in these patients [71]. While these findings suggest improved seizure control over time with RNS, it is important to recognize that RNS outcomes beyond 3 months do not reflect randomized controlled data. Adverse events in the trial included hardware site infection (5.2 %), headache (10.5 %), dysesthesia (6.3 %), and increase in generalized (4.7 %) or complex partial (5.8 %) seizures, and other complications were rare [71, 92]. Serious adverse event rates did not differ between patients receiving therapeutic or sham stimulation.

Recently, long-term outcomes with RNS have also been reported [12]. During postimplant years 3 to 6, median percent seizure reduction ranged from 48 to 66 %, although the responder rate remained relatively unchanged at 59–61 %. Overall, data do suggest a trend toward improved seizure outcome over time with RNS [12, 71]. After 5.4 years mean follow-up, the most common treatment-related complications included device site infection involving soft tissue (9 %) and explantation of the neurostimulator (5 %) [12]. Neuropsychological outcomes have also been examined in these RNS trial patients. No significant neurocognitive declines have been reported during the first 2 years of treatment, and improved neuropsychological parameters were observed in some instances [85]. Specifically, small improvements in naming abilities were reported in patients with FNE, while small improvements in verbal learning were observed in individuals with MTLE. No new adverse changes in mood have been reported in this RNS patient population, and 44 % of individuals reported meaningful improvement in quality of life after 2 years of treatment, compared to 16 % of patients who reported a decline [90].

Overall, RNS appears safe, and many patients do experience clinical improvement after 1 to 2 years of therapy, although benefits may be marginal in the first few months of treatment. Tailored responsive stimulation therapy for epilepsy is an important area of research, given potential benefits over open-loop stimulation treatments, such as fewer side effects and improved device battery life [55, 92]. Furthermore, RNS outcomes in patients who have already failed resective surgery will require further study. Broader clinical use of RNS will be dependent on further study and continued improvements in this technology.

Disconnection procedures

Even prior to laser or radiosurgical ablation techniques, or the development of neurostimulation devices for neuromodulation, disconnection procedures for epilepsy have been explored, with the goal of limiting seizure spread and reducing morbidity. Two relatively common disconnection procedures that continue to be utilized in many epilepsy surgery practices include MST and CC. Large-scale disconnection procedures for catastrophic hemispheric epilepsy syndromes, such as functional hemispherectomy or hemispherotomy, are not included here, but have been recently discussed [41]. Complete seizure freedom is rare with disconnection procedures alone.

Multiple subpial transections

MST was introduced by Morrell in 1989 as a targeted disconnective procedure for patients with an EZ localized to eloquent neocortex, such as that subserving speech, vision, and primary motor and sensory function [91]. The procedure involves numerous parallel subpial incisions applied to involved cortex to severe tangential intracortical fibers and is based on evidence suggesting that epileptic spread requires horizontal cortico-cortico connections, while most functional neuronal signals travel vertically in cortical columns [6, 91]. Modification of the original technique, utilizing radiating

MST with a single cortical incision, guided by electrocorticography and neuronavigation, has also recently been described [94]. While eloquent cortex is typically targeted with MST, multiple hippocampal transection has also been described as a potentially verbal memory-preserving surgical approach for the treatment of unilateral MTLE [99].

MST has been associated with low risk of neurological compromise [117, 136], but its adoption as a tool for seizure control has been inconsistent. In 2002, Spencer and colleagues performed an analysis of 211 patients undergoing MST at six centers and found that 62–71 % obtained an "excellent" seizure outcome (>95 % reduction in seizure frequency) with the use of MST alone, and 87 % of patients achieved this outcome when MST was combined with resection [117]. No significant response predictors were identified in this study. Of note, other groups have described more modest results, particularly in children, with 33–46 % of patients reaching Engel class 1 or II outcome after MST without associated resection [11, 13, 100]. Recently, Downes and colleagues observed no difference in seizure status among epilepsy patients with Landau-Kleffner syndrome who underwent MST targeting the posterior temporal lobe versus those who did not undergo intervention [30]. Also, late seizure recurrence in patients with initially favorable outcomes after MST has been described [95]. Given these mixed experiences, and a lack of controlled data, a large prospective investigation of MST in treating patients with eloquent seizure foci would be valuable.

Corpus callosotomy

Callosotomy, a partial or complete division of the corpus callosum, was introduced as a palliative surgical treatment for epilepsy by Van Wagenen and Herren in 1940 [124]. By destroying the major commissural connection between the two hemispheres, callosotomy prevents contralateral spread of focal seizure activity and thus averts ictal loss of consciousness and drop attacks (tonic and atonic seizures) [5, 124]. While many investigators have suggested that only anterior callosotomy is necessary to achieve clinical benefit, others advocate for a complete callosotomy [87]. One group has recently proposed performing a callosotomy using an endoscopic approach [114].

While disconnection or "split-brain" syndromes have been a classic fear with callosotomy, postoperative debilitation is rare [76, 88]. Complete seizure freedom is also rare after this procedure, but a decrease in the frequency of incapacitating seizures is typically reported [25, 69, 86, 115]. In one large pediatric patient series, a complete arrest of drop attacks was reported in 67 % of children after partial anterior callosotomy and in 91 % of those receiving complete callosotomy [113]. However, long-term results suggest that only 35 % of callosotomy patients remain free of drop attacks 5 years after surgery, although the frequency of these seizures remains reduced in most patients [98, 119]. Callosotomy utilization has decreased since the introduction of VNS, which also helps prevent tonic and atonic seizures, though there is disagreement regarding which intervention has the best efficacy/risk profile for this purpose [1, 26, 108, 138, 139]. One recent systematic review suggests that callosotomy may be more effective than VNS in reducing atonic seizure frequency [105]. It has also been proposed that both therapies may be employed together in certain patients with particularly debilitating drop attacks [64]. In summary, although the clinical benefits of callosotomy are more modest than resective epilepsy surgery, it remains a useful tool in select patients with incapacitating drop attacks, particularly as an alternative to or after failure of VNS. Callosotomy outcomes in patients who have already failed open resection are lacking, and this topic is worthy of further study.

Discussion and conclusions

Compared to individuals without epilepsy, individuals with drug-resistant epilepsy suffer from increased morbidity and a higher rate of mortality [116, 121, 129], as well as neuropsychological and neurocognitive deficits and diminished quality of life [32, 39, 73]. Thus, continued improvements in surgical treatments for epilepsy are critically needed. Surgical resection remains the gold standard treatment for intractable epilepsy, but it is typically not performed in patients with poorly localized seizures, multifocal EZs, or an EZ which co-localizes with eloquent cortex. Furthermore, some patients harbor significant risk factors for an open surgical procedure or are averse to it. While resection for epilepsy is safe, with approximately 2 % significant morbidity and 0.24 % surgical mortality [116, 121, 129], further improvements in the safety profile of invasive epilepsy treatments are needed. For these reasons, nonresective procedures for intractable seizures are becoming increasingly important in the treatment of this disorder.

Seizure outcomes and advantages/disadvantages of nonresective procedures discussed in the present review are summarized in Tables 1 and 2, respectively. Importantly, while ablative treatment options such as SLA and SRS may replace resection in certain cases, current neurostimulation and disconnection procedures remain palliative and should not be considered replacements for resection. Seizure freedom is the single most important predictor of quality of life in epilepsy, but complete seizure freedom is dramatically less common with neuromodulation or disconnection procedures compared to open resection. While seizure freedom rates with ablative techniques also remain inferior to resection, continued improvement in our understanding and application of these technologies will hopefully lead to progressive improvements in

Table 1 Summary of seizure outcomes after nonresective surgery for epilepsy

Treatment	Seizure outcomes	Follow-up (months)	Example references
(A) Ablative procedures			
Stereotactic laser ablation (SLA)	36–54 % seizure free	12–14	[31, 77, 84, 133]
Stereotactic radiosurgery (SRS)	69–77 % seizure free	24–36	[7, 17, 137]
(B) Neurostimulation procedures			
Vagus nerve stimulation (VNS)	51–63 % reduced frequency; 51–57 % response rate	12–24	[3, 28, 43, 52, 110]
Deep brain stimulation (DBS)	41–69 % reduced frequency; 43–68 % response rate	12–60	[54, 109]
Responsive neurostimulation (RNS)	44–66 % reduced frequency; 44–59 % response rate	12–72	[12, 71]
(C) Disconnection procedures			
Multiple subpial transections (MST)	33–71 % (near) seizure free; higher when combined with resection	>12	[11, 13, 100, 117]
Corpus callosotomy (CC)	35–91 % reduced frequency of drop attacks	>12	[98, 105, 113, 119]

Outcome measures differ between interventions, as seizure freedom is the primary treatment goal in ablative procedures (A), while reduction of seizure frequency is more often the goal with palliative neurostimulation procedures (B). Many MST outcomes have reported "near" seizure freedom rates, while the primary goal of callosotomy is reduction of drop attacks (C)

seizure outcomes with minimally invasive interventions for epilepsy.

Cost effectiveness research has suggested that resective epilepsy surgery is more economically effective than continued medical therapy in both children and adults [14, 111, 128], but few cost effectiveness studies have examined nonresective epilepsy procedures. Ben-Menachem et al. performed a retrospective analysis of 43 patients receiving VNS for epilepsy and concluded that VNS results in annual reduction of approximately 3000 dollars (in 2002 US currency) in unplanned hospital costs per patient [9]. Helmers and colleagues performed a retrospective analysis of US Medicaid data and concluded that VNS is associated with cost savings and decreased use of resources in children with intractable epilepsy, as compared to medical therapy alone [72]. However, cost analyses of most other nonresective epilepsy procedures, including ablation and stimulation techniques, have not yet been reported.

One important goal in the development of novel therapies for intractable epilepsy is to increase the number of patients who are candidates for or amenable to treatment. Less than 5 % of patients with drug-resistant epilepsy—which is defined after the failure of two or more antiepileptic drug trials—enter remission each year with continued medical therapy alone [21, 58, 80, 81, 121, 130]. Therefore, the American Academy of Neurology, the American Association of Neurological Surgeons, the National Association of Epilepsy Centers, and the International League Against Epilepsy all agree that individuals who have failed two or more antiepileptic medications should be referred to a comprehensive epilepsy center for surgical evaluation [24, 35, 82]. Unfortunately, the utilization

Table 2 Advantages and disadvantages of nonresective epilepsy procedures

Treatment	Advantages	Disadvantages
(A) Ablative procedures		
Stereotactic laser ablation (SLA)	May be curative; less invasive than resection	Appears less efficacious than resection
Stereotactic radiosurgery (SRS)	May be curative; less invasive than open surgery	Delayed benefit of 1–2 years
(B) Neurostimulation procedures		
Vagus nerve stimulation (VNS)	No intracranial surgery; EZ localization not necessary	Palliative; complete seizure freedom is rare; implanted hardware
Deep brain stimulation (DBS)	EZ localization not necessary	Palliative; requires intracranial hardware; not closed loop
Responsive neurostimulation (RNS)	Can treat eloquent EZ; closed loop	Palliative; requires intracranial hardware; EZ localization is necessary
(C) Disconnection procedures		
Multiple subpial transections (MST)	Can treat eloquent EZ; no implanted hardware	Efficaciousness remains unclear; risk of neurological deficit
Corpus callosotomy (CC)	Relatively efficacious for atonic seizures; no implanted hardware	Palliative; only useful for patients with atonic seizures

EZ epileptogenic zone

of resection for epilepsy remains dramatically underutilized, with only a minority of potentially eligible candidates receiving surgical treatment each year [33, 36, 38, 47, 48, 68]. In the near future, it will be important to study whether novel nonresective surgical options for epilepsy will increase the number of patients who receive treatment—or at the very least stimulate more referrals to centers where patients can receive a comprehensive evaluation. Such referrals are critical, given the significant deleterious effects of recurrent seizures on quality of life and survival in patients with epilepsy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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Comments

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Englot et al. review the current state of the art in nonresective epilepsy surgery. This paper has to be considered as continuation of the previous paper of the authors that focused on resective epilepsy surgery (1). The conclusions of these two reviews are that resective surgery provides more than 50 % complete seizure control while nonresective surgery has palliative goals and improve seizure control. This is particularly true for neuromodulation techniques (VNS, DBS, RNS) and disconnection surgeries (callosotomy and subpial transections). On the other hand, ablative surgeries (SLA, SRS) especially in temporal lobe epilepsy could achieve similar results than resective surgery. The full armamentarium of epilepsy surgery techniques is a prerequisite for adequate treatment of patients with drug-resistant epilepsies.

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1. Englot DJ, Chang EF. Rates and predictors of seizure freedom in resective epilepsy surgery: an update. Neurosurg Rev 37(3):389–404

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Englot et al. have presented a literature review of seizure outcomes in nonresective epilepsy surgery. The gold standard in drug-resistant epilepsy is still appropriate presurgical evaluation of potential epilepsy surgery candidates in a tertiary comprehensive epilepsy care center and to subject them to appropriate surgical therapy. The seizure freedom rate of resective surgery is about 80 % in the literature. These patients can expect to be off medication in about 5 years from the date of surgery. The recent therapies like ablation and stimulation procedures may be appealing but there are caveats. They lack long-term outcome data analysis. Procedures like SRS take about 8 to 12 months for any tangible effect. The seizure freedom is still inferior to resective surgery. The long-term side effects are also not known. These procedures can be considered for patients who are averse to surgical resection, had a failed resective surgery, or at high risk due to major illnesses or advanced age. In these patients, palliation may be still worthwhile. In the current situation, even SLA and SRS may be unlikely to replace resection procedures. In resource-constraint countries, still cost effectiveness is an important variable. Resective or palliative surgical procedures (like multiple subpial transections and corpus callosotomy) are still cost effective than any nonresective modality. Large multicentric randomized double-blind studies are necessary and long-term outcome data will only decide their efficacy. The authors have presented a concise review, which is lucid, informative, and well referenced.