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Brief Communication

Resective epilepsy surgery involving eloquent cortex in the age of responsive neurostimulation: A value-based decision-making framework

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ABSTRACT

Resective epilepsy surgery has endured as the most effective way to render patients with seizure-free intractable localization-related epilepsy. Under conditions where the seizure focus is in close proximity to eloquent cortex, a postoperative deficit may be expected. Patients often accept the risk or certainty of these deficits for the possibility of seizure freedom. Recently, responsive neurostimulation (RNS) has emerged as an alterative to resective epilepsy surgery. This cranially implanted closed-loop neurostimulation system records brain activity and interrupts seizure propagation, thereby decreasing seizure frequency. The introduction of RNS to clinical practice raises several challenges to clinicians and patients alike. Despite a dearth of long-term data, should this be considered as a safer and potentially reversible option for patients who would otherwise be candidates for resective surgery in eloquent cortex? In the current report, we analyze the complex bioethical implications of presenting a new, "safer" technology, alongside a well-established, "more effective" treatment. We present an adapted value-based decision-making model to guide patients and help clinicians navigate the tradition of resective epilepsy surgery in eloquent cortex in the nascent age of RNS.

1. Introduction

The World Health Organization identified epilepsy as the most common serious neurologic condition affecting children, with many patients suffering from symptoms as adults [1]. It is estimated that up to 30% of patients with epilepsy have inadequate seizure control on at least two antiseizure drugs at maximal tolerated doses for 18–24 months [2]. This form of severe epilepsy is termed drug-resistant epilepsy (DRE), and affected patients have less than a 5% chance of responding to further medical treatment [3]. Patients with DRE may be suitable candidates for resective surgery, which has the potential to control seizures and often render patients seizure-free [4]. Resective surgery is not without risks, particularly in circumstances when resections are proposed in eloquent brain regions, where a postoperative deficit may be anticipated.

Eloquent cortex includes any brain area that is involved in language ability, memory, somatic and special sensory processing, or movement. Commonly identified areas include the bilateral motor and sensory cortices, internal capsule, basal ganglia, hypothalamus and thalamus, occipital lobes, brainstem, dentate nucleus, and often the left temporal and frontal lobes and hippocampus [5,6]. In practice, however, the definition of eloquence is more elusive. Individual values, customs, and beliefs modify the importance placed on these and other brain functions, such as advanced cognitive processing, attention, and behaviour.

The Rolandic region is the prime example of an eloquent area commonly mapped with a two-stage epilepsy surgery to determine whether and to what extent a motor deficit may manifest following surgical resection. In twenty-two children who received resective epilepsy surgery that involved primary motor and/or sensory cortex, 20 patients developed varying degrees of hemiparesis [7]. With more conservative resections of 48 children with intractable epilepsy secondary to a Rolandic lesion, 20 patients (41.6%) demonstrated transient neurological deficits [8]. A separate series of fifty-two patients of all ages with peri-Rolandic transections or resections reported persistent neurological deficits in 26 patients (50% of the study population) [9]. Understandably, resective surgery in the precentral and postcentral gyri results in expected morbidity immediately

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postoperatively. These may be transient, particularly in younger patients, who may regain lost functions over time [7].

The morbidity of resective surgery in eloquent cortex is often offset by the benefits of potential seizure-freedom. The effectiveness of resective surgery in the Rolandic cortex is favorable with 46–81% of patients demonstrating Engel Class 1 or 2 at long-term follow-up [8,9]. The morbidity of transient hemiparesis or speech difficulties may be worthwhile if surgery provides a desirable seizure outcome, yet these decisions are often complex and value-laden.

Neurostimulation is an option for patients who have DRE localized to eloquent cortex. While various devices have been available for a long time, including vagus nerve and deep brain stimulation, responsive neurostimulation (RNS) has been approved recently in 2013 in adult patients with DRE localized to one or two epileptogenic foci [10]. This is a closed-loop neurostimulation system that uses a cranially implanted neurostimulator to record brain activity and then provides brief pulses of electrical stimulation through the leads to interrupt seizure propagation. The surgery involves insertion of depth and/or subdural cortical strip leads placed at a patient's seizure focus. The prospective, multicenter, double-blinded, randomized, sham-stimulation-controlled pivotal study demonstrated a significant reduction in seizure frequency in the treatment group of 37.9% compared to the sham group (17.3%, $p = 0.012$) [11].

2. Shared decision-making

When patients are presented with differing options, decision-making is often a daunting task. Clinician and patient must engage in bidirectional, honest, and detailed conversations as both parties are stakeholders in the process. Only the patient can share their subjective experience with epilepsy, including current frustrations with seizures, limitations in daily life, and their values on what would be an ideal and more importantly acceptable outcome. Only the physician can gather all the clinical data to provide accurate yet comprehensible options. A suitable discussion will require time, honesty, and likely more than one clinic visit.

The decision-making is further complicated by the fact that some patients with epilepsy may not be capable to make their own decisions. Many patients with DRE often present with debilitating seizures and progressive, secondary cognitive or developmental delay is common [7,8]. Furthermore, there are many children or adolescents seeking surgical opinions for epilepsy surgery, including RNS. The introduction of a substitute decision-maker adds an additional layer of complexity.

We present four important issues to consider in decision-making regarding surgery for epilepsy surgery in eloquent cortex: (a) weighing the goals of treatment between higher likelihood of seizure freedom with greater morbidity versus “safer” seizure reduction, (b) known and unknown long-term outcomes, (c) the reversibility of the two technologies and the timing of each treatment in combination or alone, and (d) access to each respective treatment. (Fig. 1)

2.1. Goals of treatment

To understand the goals of treatment, it is important to recognize the patient's objective neurological baseline, and also, his/her subjective experience with epilepsy. In some cases, very severe seizures may result in a motor, sensory, or cognitive deficit prior to any treatment. In such cases, treatment goals should weigh the expected seizure outcomes against the expected functional deteriorations. A patient with good presurgical motor function may be poorly served by a the risk of hemiparesis or hemiplegia [8,9]. Conversely, a patient with premorbid hemiparesis may not be functionally limited by resection of Rolandic cortices.

In addition to the expected functional limitations as a result of disruption of eloquent cortex, families and patients must further consider the functional benefits associated with improved seizure control. These include the ability to maintain gainful employment, driving, independence, socializing, and freedom from antiseizure medications [12]. Some of these may be achieved not exclusively through seizure-freedom, but also with seizure reduction or given lesser severity of seizures. In this context, RNS may not render a patient seizure-free, but could potentially successfully realize some of the patient's or families' goals. Indeed, in the initial RNS cohort, there were statistically significant improvement in quality of life in both 1 and 2 years after implantation in 10 of the 17 primary scores, including seizure worry, health discouragement, attention and concentration, work, and language [13].

2.2. Long-term outcomes

Responsive neurostimulation is a relatively new treatment, raising several concerns about sustained efficacy and unknown long-term outcomes. The safety assessment was conducted on sixty-five subjects, demonstrating 6.2% serious adverse events in the first month postimplant and 9.2% in the first 3 months [10]. After the blinded period, 59 patients demonstrated 44% seizure reduction at 1 year and 53% at 2 years in the open-label period [13].

Conversely, resective epilepsy surgery is a well-established technique, supported by large case-controlled studies as well as several randomized control trials, with a long history of success. Much earlier to the pivotal randomized trial on temporal lobe epilepsy in 2001 [14], surgeons identified cortical resection as a safe and effective treatment for focal epilepsy in the early 1900's [15]. Resective epilepsy surgery can produce seizure-freedom in 34–81% of patients in adults and children, with the best outcomes in temporal lesions, and patients with hippocampal sclerosis or benign tumors, with a perioperative mortality of 0.1–0.5% [16,17].

In addition to the unknown long-term outcomes of RNS, presurgical discussions should also discuss the fact that this technology, unlike resective procedures, requires long-term surveillance and maintenance. Repeat cranial procedures are required to change the pulse generator and potentially to troubleshoot the system. Decisions regarding the optimal treatment should project forward to better define how the intervention will affect the patient in the long term.

2.3. Reversibility and timing of treatments

Responsive neurostimulation and resective surgery also differ immensely in their reversibility. When comparing resective surgery of eloquent cortex and RNS, patients need to understand that RNS is an implantable device that is both reversible and removable. If device-related complications arise, including breakage of wires, infections, or undesirable neurologic effects, the RNS implant can be removed. Furthermore, both the positive and negative consequences of RNS are at least theoretically reversible. Resective surgery will have a permanent impact. Although there may be improvement of functional deficits after surgery namely from postoperative edema or retraction, any loss of the eloquent cortex will result in permanent loss of function. Patients' risk profiles, analysis of risk–benefit for each individual, and confidence in the treatment and its reversibility are all important factors to keep in mind.

One option is to adopt a strategy to perform the reversible procedure upfront with the permanent resective surgery at a later date, should RNS prove disappointing. Unfortunately, there are no good data to compare resections after failed RNS with early surgical resection. Risk-averse patients may easily choose RNS because its effects are reversible and resective surgery is still a future consideration. Conversely, a repeat cranial procedure may be associated with more risks, including bleeding, cortical injury due to arachnoid scarring and wound healing complications. The decision to proceed with RNS upfront must therefore be informed by the risk and benefits of a multistage approach.

There is a risk that the introduction of RNS as a first-stage approach could paradoxically result in worse outcomes for patients. This could

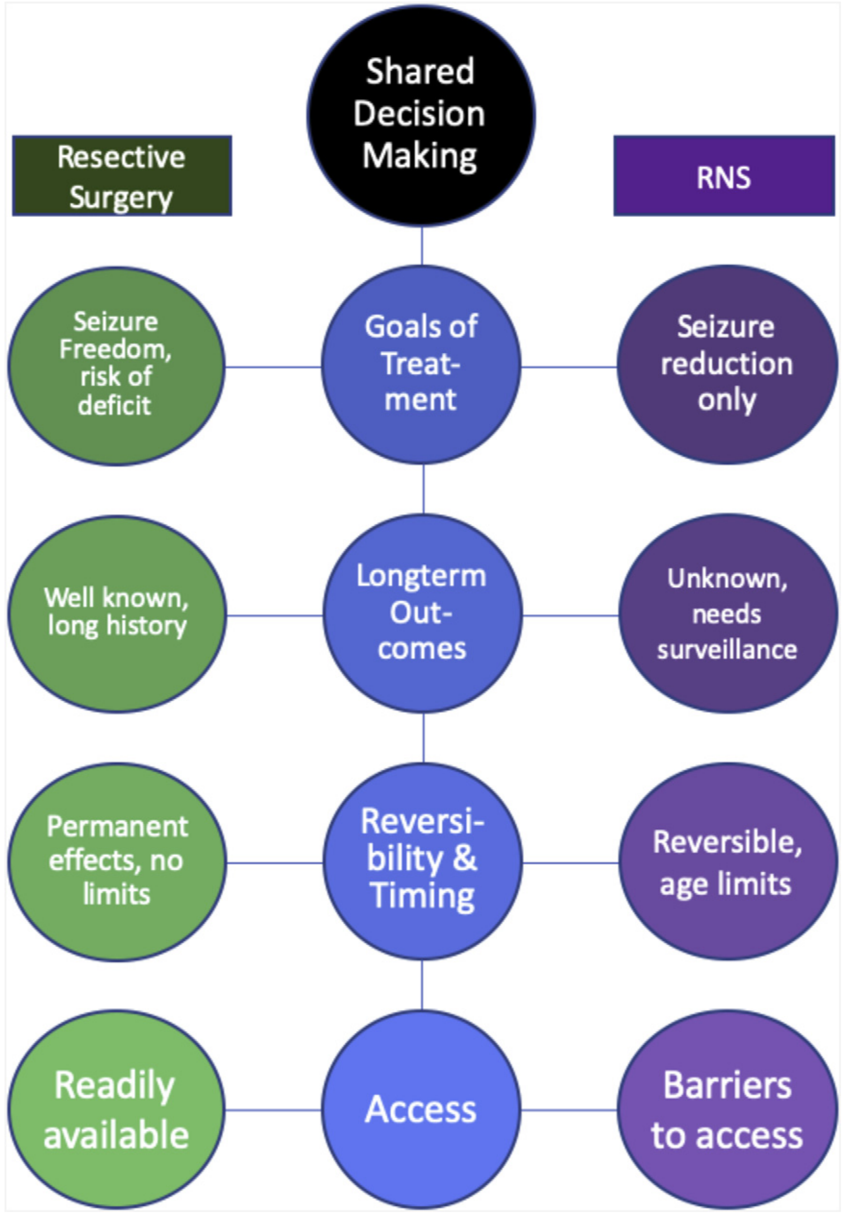

Fig. 1. Shared decision-making. In the context of surgical decision-making for patients with DRE, the four considerations are heavily values-based, requiring honest introspection from the patient. Patients need to evaluate the goals of treatment, differences in long-term outcomes, reversibility, timing, and accessibility of each treatment option.

occur if patients (and providers) are less motivated to pursue a resective surgical procedure after "failed" RNS if some benefit is observed but the patients remain disabled by ongoing seizure activity. There is a risk that patients could be denied a potentially curative procedure. In the post-surgical follow-up, clinicians should continue to explore whether any seizure reduction is "sufficient" or whether patients would want to consider resective surgery with the goal of curative seizure freedom. There should be an understanding that RNS and resective surgery are not mutually exclusive options.

In children, unique challenges also arise as there is increasing evidence that shorter durations of uncontrolled epilepsy facilitates better seizure and developmental outcomes, as epilepsy interferes with normative brain development [18]. A current contraindication for RNS is inadequate skull thickness, and therefore younger children would not be able to receive the implant. An additional layer of complexity is introduced when deciding whether to wait for the child to be a candidate for RNS and potentially compromise critical windows for brain development or to proceed with resective procedures in the eloquent cortex, given their propensity for functional recovery at younger ages.

2.4. Access to technology

The development of any technology, but even more so health technology, requires a careful socioeconomic analysis prior to societal integration and acceptance. Overall, health technology is intended to improve the quality of life of individuals, which then begs the question, "what is the good life?" The answer is of course heavily influenced by each individual's relational values and beliefs [19].

Responsive neurostimulation has only been approved in the United States for adults. The insertion and subsequent monitoring of the RNS implant are only available at select centres. Patients in Europe and Canada would have to travel to the United States not only for the initial surgery but also for follow-up appointments. New technologies are not always ubiquitously available and this inequality in access to healthcare poses another obstacle in this complex decision. If a patient receives

RNS, families and patients need to understand that their treatment, surveillance, and follow-up may require travel, additional financial support, and continued commitment to provide additional data for further research. Resective surgery is more widely available and there may be instances where this is the less desired treatment and yet the only option based on access or financial constraints. These conflicts are amplified in the resource-poor setting, but such ethical challenges are beyond the scope of the current article.

3. Decision-making model

Given the complexity of RNS as an emerging technology for a complex and multifaceted disease etiology, it becomes critical to apply a framework to decision-making when many values, concerns and personal opinions must be considered. Several models have been previously proposed. One such model attempts to provide an explanatory framework of perceptions influencing decision-making in surgery for epilepsy, identifying fear of surgery, ignorance of diagnosis or treatment options, and tolerance of symptoms as important factors patients base decisions on [20]. Recognizing the importance and complexity of the decision to undergo surgery, another study recommended having both long-form decision aids utilized outside the clinic (such as an interactive web-based educational module) and short-form decision aids utilized with clinicians (leaflets, graphics) [21]. We propose an adapted value-based ethical framework to inform decision-making in the context of epilepsy surgery in eloquent cortex (Fig. 2). It was described in public health decision-making that incorporates a value-based and pluralist approach [22]. There are five explicit steps to this approach:

1. *Identification*: Given the clinical history and diagnostic tests, identify possible treatment options for epilepsy. This step requires a multidisciplinary analysis from neurologists, neurosurgeons, psychosociologists, and social workers or linguists if applicable.
2. *Distinguishing*: Distinguish relevant empirical difference between treatments, including contingencies. Judgements should be made on known evidence and relevance to the values of the patient and/or caregivers. Patients should also share how much involvement in decision-making is desired and what they would like to know.
3. *Ranking*: Rank, as far as possible, alternatives from best to worst. This may be based on personal goals, cultural values, or health objectives, etc.
4. *Evaluation*: Make explicit, as far as possible, in what sense some treatments are better than others. The patient should identify which factors ultimately influence the decision.
5. *Documentation and Review:* Submit the result of the evaluation and plan for reevaluation. If possible, a patient of appropriate age and capacity should be given the time and education to understand the treatment decisions.

Fig. 2. Decision-making model. This five-step value-based framework will help patients evaluate their options and provide structure to make complex decisions.

The first two steps of this framework are rather analogous to a typical consent conversation. A systematic and rigorous synthesis of the data and treatment options is presented in the context of the patient's subjective experience with the illness. The third step of the algorithm, ranking, is facilitated by explicitly identifying the values, objectives and goals of patients and how they may be realized through surgical interventions. Often, different treatments prioritize different values and goals; these conflicts can be further explored to determine which treatment is most favorable. Lastly, the final processes of evaluation and reevaluation permit acceptance or rejection of the proposed plan. In the context of innovative technologies with several unknown factors, this values-based approach provides a foundation for decision-making.

In the following segment, we provide three illustrative cases highlighting the utility of the value-based decision-making approach in informing decisions regarding epilepsy surgery in the eloquent cortex.

3.1. Case 1

A 4 year-old boy presents to clinic with his parents. He has been suffering from severe epilepsy that has been refractory to medical treatment for 3 years. He has daily left sided sensorimotor seizures followed by long postictal unresponsiveness, frontocentrotemporal electroencephalogram (EEG) spikes, magnetoencephalography (MEG) shows Rolandic-Sylvian spikes with abnormal magnetic resonance imaging (MRI). At baseline, he does not have any sensory or motor deficits. The MRI demonstrates an identifiable lesion in the right motor cortex, concordant with the EEG findings. The team believes this patient will have a good seizure outcome after surgery if invasive monitoring can inform a resective procedure. He has global developmental delay and he is preparing to enter kindergarten later this year. His seizure frequency is increasing and causes him and his parents immense psychological distress.

First, we *identify* the possible treatment options of (a) continued medical treatment, (b) resection of right-side Rolandic lesion after invasive monitoring, or (c) RNS. Second, we *distinguish* on one hand the unknown long-term effects of RNS, particularly in this age range, and on the other hand the high likelihood of neurologic motor deficits of resective surgery. Furthermore, the possibility of resection after failed RNS, and whether this is less optimal than upfront resection both in terms of surgical risks and critical windows for brain development in the interval between the procedures. The initial *ranking* of options are i) resective surgery, ii) RNS, with possibility of resection after failed RNS. Jointly, the circle of care decides against continued medical treatment and decides to proceed with upfront resective surgery. The values of the patient and his family justifies the *evaluation* that resective surgery is warranted because of this young boy's ability to tolerate a motor deficit, the possibility of regaining motor function as he is young, and the current distress of daily seizures and episodes of unresponsiveness impacting his ability to participate in school. The family and the physician team will reapproach this decision at a second clinic visit to *review* the decision and to answer additional questions.

3.2. Case 2

A 16 year-old girl with longstanding right side hemiparesis is seeking treatment options for her daily sensorimotor seizures. She has been investigated with MRI, EEG, MEG, and treated with antiseizure medication for 10 years. Her EEG shows multifocal spikes with a suspected origin within the left Rolandic region, and her MRI is normal. Seizure outcome is difficult to predict based on current findings. Although her right arm has distal weakness, she is able to participate in school and perform nondexterous tasks with an orthotic aid (writing, eating with a spoon, picking up certain objects).

First, the treatment options *identified* are (a) continued medical treatment, (b) resection of left pericentral gyri, or (c) RNS. This patient has a difficult choice. The clinical team helps her *distinguish* that RNS will spare her remaining motor function if she can accept a reduction and not a complete cessation of her seizures, whereas resective surgery can potentially achieve a cure from epilepsy and she has already learned to cope with a motor deficit, which may worsen after a resective procedure. She may choose to *rank* i) RNS, ii) resective surgery after failed RNS, and she still considers iii) continued medical treatment. In her *evaluation* of options, she believes she is risk-averse and would prefer a treatment that has reversible effects. Furthermore, she considers that until she knows her career trajectory, she does not want to risk further motor deficits at her age. She decides to pursue RNS. She documents her ranks and evaluations for a *review* at a later date after discussions with her friends and family.

3.3. Case 3

A 24 year-old woman living in a rural setting with no neurologic deficits has weekly sensorimotor seizures that adversely affected her quality of life. Her MRI is normal, but her EEG suggests a pericentral epileptogenic focus. She underwent stereoelectroencephalography which confirmed the epileptogenic zone within the primary motor cortex.

Treatment options are *identified* as (a) continued medical management or (b) consideration of RNS. In this situation, resective surgery may not be recommended given her good clinical status and relatively mild severity of seizures as well as the expected postoperative deficit. The *distinguishing* factors she considers are that RNS is still a novel technology with unknown long-term benefits, and she would need to make multiple physician visits to an urban centre to program the device. She will need to travel out of state for her treatments and follow-up. The patient *ranks* RNS over continued medical treatment. She *evaluates* that she does not like the side-effects of her antiseizure medications and would like to trial methods of seizure reduction with minimum risk despite obstacles to access her care. The clinical team asks her to meet her treatment team out of state for her *review* of her treatment goals.

4. Conclusions

Epilepsy is a common yet challenging condition with multiple ethical consideration that arise at multiple treatment decision points. Bioethical issues in epilepsy are particularly salient given the priority given to diseases that could affect an individual's agency and pose a threat to their development, quality of life, and possibly behaviour. Diagnostic and treatment options are often subjective and must factor a patient's experience with epilepsy. Although resective surgery in eloquent cortex carries a higher risk for neurologic deficit, it is an established and effective treatment. Conversely, RNS is reversible and may be a “safer” upfront alternative. In order to navigate the complex ethical landscape, it is imperative for clinicians to be both honest and comprehensive with patients and caregivers. To facilitate these conversations, we propose a value-based framework to inform the conduct of resective epilepsy surgery in the age of RNS.

Declaration of competing interest

There are no conflicts of interests for both authors.

References

[1] Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord 2015;17:117–23.
[2] Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: a systematic review and meta-analysis. Epilepsia 2018;59:2179–93.
[3] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
[4] Go C, Snead 3rd OC. Pharmacologically intractable epilepsy in children: diagnosis and preoperative evaluation. Neurosurg Focus 2008;25:E2.
[5] Nakai Y, Jeong JW, Brown EC, Rothermel R, Kojima K, Kambara T, et al. Three- and four-dimensional mapping of speech and language in patients with epilepsy. Brain 2017;140:1351–70.
[6] Sawaya R, Hammoud M, Schoppa D, Hess KR, Wu SZ, Shi WM, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 1998;42:1044–55 [discussion 1055-6].
[7] Benifla M, Sala Jr F, Jane J, Otsubo H, Ochi A, Drake J, et al. Neurosurgical management of intractable rolandic epilepsy in children: role of resection in eloquent cortex. J Neurosurg Pediatr 2009;4:199–216.
[8] de Oliveira RS, Santos MV, Terra VC, Sakamoto AC, Machado HR. Tailored resections for intractable rolandic cortex epilepsy in children: a single-center experience with 48 consecutive cases. Childs Nerv Syst 2011;27:779–85.
[9] Pondal-Sordo M, Diosy D, Tellez-Zenteno JF, Girvin JP, Wiebe S. Epilepsy surgery involving the sensory-motor cortex. Brain 2006;129:3307–14.
[10] Sun FT, Morrell MJ. The RNS system: responsive cortical stimulation for the treatment of refractory partial epilepsy. Expert Rev Med Devices 2014;11:563–72.
[11] Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295–304.
[12] Taylor DC, McMacKin D, Staunton H, Delanty N, Phillips J. Patients' aims for epilepsy surgery: desires beyond seizure freedom. Epilepsia 2001;42:629–33.
[13] Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS system pivotal trial. Epilepsia 2014;55:432–41.
[14] Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness, Efficiency of Surgery for Temporal Lobe Epilepsy Study G. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345:311–8.
[15] Krause F. Surgery of the brain and spinal cord based on personal experience. New York, NY: Rebman; 1912.
[16] Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA 2015;313:285–93.
[17] Engel Jr J, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al, Early Randomized Surgical Epilepsy Trial Study G. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 2012;307:922–30.
[18] Dwivedi R, Ramanujam B, Chandra PS, Sapra S, Gulati S, Kalaivani M, et al. Surgery for drug-resistant epilepsy in children. N Engl J Med 2017;377:1639–47.
[19] Hofmann BM. Why ethics should be part of health technology assessment. Int J Technol Assess Health Care 2008;24:423–9.
[20] Dewar SR, Pieters HC. Perceptions of epilepsy surgery: a systematic review and an explanatory model of decision-making. Epilepsy Behav 2015;44:171–8.
[21] Pickrell WO, Elwyn G, Smith PE. Shared decision-making in epilepsy management. Epilepsy Behav 2015;47:78–82.
[22] Grill K, Dawson A. Ethical frameworks in public health decision-making: defending a value-based and pluralist approach. Health Care Anal 2017;25:291–307.