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MODERN SURGICAL STRATEGIES IN DRUG-RESISTANT EPILEPSY: RESECTION OF EPILEPTIC FOCI, MINIMALLY INVASIVE METHODS, AND NEUROSTIMULATION

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ABSTRACT

Introduction: Drug-resistant epilepsy (DRE) affects approximately one-third of patients with epilepsy and represents a significant clinical challenge. When adequate seizure control cannot be achieved with antiseizure medications, alternative therapeutic strategies, including surgical and neuromodulatory approaches, must be considered to reduce seizure burden and improve quality of life.
Methodology: This review is based on an analysis of contemporary scientific literature focusing on surgical, minimally invasive, and neuromodulation-based treatments for drug-resistant epilepsy. Studies published in recent years were reviewed to evaluate treatment efficacy, safety profiles, and long-term outcomes.
Results: Resective surgery, particularly anterior temporal lobectomy and selective amygdalohippocampectomy, remains one of the most effective treatment for appropriately selected patients, achieving long-term seizure freedom in approximately 60–70% of cases. Minimally invasive techniques such as laser interstitial thermal therapy (LITT) and stereotactic radiosurgery (Gamma Knife) offer favorable seizure outcomes with reduced morbidity and shorter hospitalization. Neuromodulation methods, including vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation, provide significant seizure reduction and improved quality of life in patients who are not candidates for resective surgery.
Conclusion: The management of drug-resistant epilepsy requires an individualized, multidisciplinary approach. Advances in minimally invasive surgery and neuromodulation expand therapeutic options, allowing for tailored treatment strategies that balance efficacy and safety. Continued research and technological development remain essential to optimize outcomes for patients with DRE.

KEYWORDS

Drug-Resistant Epilepsy, Epilepsy Surgery, Focal Resection, Seizure Control, Innovative Therapies

CITATION

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1. Introduction

1.1 Epilepsy is a long-term neurological condition that affects more than 50 million people around the world [1]. Approximately one-third of people with epilepsy do not achieve seizure control despite taking one or more antiepileptic drugs, which meets the criteria for drug-resistant epilepsy (DRE) [2]. Its nature includes the occurrence of unprovoked seizures [3]. Recent scientific reports indicate a significant association between drug-resistant epilepsy and specific neurological syndromes, such as tuberous sclerosis complex (TSC), Lennox-Gastaut syndrome (LGS), and Dravet syndrome [4]. According to current hypotheses regarding the mechanisms of drug resistance in epilepsy, the lack of seizure control by antiepileptic drugs results from changes in the structure and/or function of their molecular targets. Consequently, effective treatment of patients with drug-resistant epilepsy requires an approach that targets a variety of molecular targets, including voltage-gated sodium channels (VGSC) and γ-aminobutyric acid (GABA) receptors[1]. Traditional first-line treatment of drug-resistant epilepsy involves the use of pharmacological therapy. There are three generations of antiepileptic drugs: older, well-known first- and second-generation drugs, and newer third-generation drugs, which have been on the market since the late 1990s. First-generation antiepileptic drugs include the oldest pharmaceuticals such as phenobarbital, phenytoin, primidone, and ethosuximide.

Second-generation drugs include benzodiazepines, carbamazepine, and valproates. The third and newest generation of antiepileptic drugs includes vigabatrin, zonisamide, lamotrigine, felbamate, gabapentin, topiramate, fosphenytoin, tiagabine, oxcarbazepine, and levetiracetam.

According to the latest research, anticonvulsant drugs introduced to the market several years ago, such as briwaracetam, cannabidiol, cenobamate, everolimus, and fenfluramine, have a significantly better therapeutic profile than drugs used in previous years, although they are not free from side effects.

Contemporary epilepsy treatment strategies focus not only on introducing innovative drugs, but also on improving existing anti-epileptic therapies. In recent years, rescue formulations for use outside the hospital have been developed, enabling rapid termination of seizures and prevention of status epilepticus. Until 2018, the only such drug was rectal gel containing diazepam. Since 2019, the FDA has also approved midazolam and diazepam in intranasal form, which provides a faster therapeutic effect and is better tolerated by society compared to the previously used rectal gel. In Europe, rapidly absorbed buccal midazolam has also been available since 2011, and other forms, including buccal diazepam and inhaled alprazolam, are also being studied. Oral rescue forms are widely used, but they have limitations related to absorption, the risk of aspiration, and patient cooperation, which may affect further treatment of the underlying disease. [5]

In patients with drug-resistant epilepsy (DRE), surgical interventions are more effective in controlling seizures than long-term pharmacotherapy alone. Currently, surgical treatment is the primary therapeutic strategy for this group of patients.[6]

These include both resective surgical techniques, using neurosurgery, and neuromodulation methods, such as deep brain stimulation (DBS) or vagus nerve stimulation (VNS). Of all neuromodulation strategies, invasive vagus nerve stimulation (i-VNS) is the most commonly used, involving the implantation of a stimulator connected to an electrode placed on the vagus nerve. [3]

Preoperative assessment of patients with drug-resistant epilepsy (DRE) plays a key role in planning surgical treatment. It allows for the determination of possible modifications to the procedure and the development of an optimal surgical plan for a given patient, thereby minimizing the risk of postoperative complications. Preoperative assessment focuses on determining the exact location of epileptic foci, analyzing the patient's overall health, identifying potential risks associated with the procedure, and assessing the possible impact of surgery on quality of life. A thorough analysis of these factors allows the attending physician to make more accurate, personalized treatment decisions.

Surgical methods used in the treatment of drug-resistant epilepsy can be divided into open techniques and minimally invasive techniques. Open surgery techniques primarily include anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH), while minimally invasive methods include laser interstitial thermal therapy (LITT), radiofrequency thermocoagulation (RFTC), and gamma knife surgery (GKS). The latest scientific reports show that the use of surgery in the treatment of drug-resistant epilepsy can reduce the frequency of seizure recurrence—approximately 58% of patients achieve seizure freedom, compared to only 8% of patients treated with medication alone—and improves quality of life. Despite the long-term use of surgery in the treatment of drug-resistant epilepsy, the effectiveness of resection and minimally invasive procedures in long-term seizure control remains a subject of lively debate. [7]

The past and surgical innovations in the treatment of drug-resistant epilepsy.

Attempts to treat drug-resistant epilepsy date back to ancient times, when trepanation of the skull was used as a treatment. In modern times, the increasingly frequent side effects of pharmacological treatment and, in many cases, the ineffectiveness of drug therapy have contributed to the development of new surgical treatment methods. [8].

Electroencephalography (EEG) was originally used as a precursor to further research into targeted surgical therapies. EEG was used to monitor changes in the brain during epileptic seizures. [8,9].

Further development of neuroimaging techniques, in particular magnetic resonance imaging, has significantly improved the planning of neurosurgical procedures and translated into better surgical outcomes. In recent years, modern, minimally invasive therapeutic methods have been introduced, such as laser interstitial thermal therapy (LITT), responsive neurostimulation (RNS), and MRI-guided transcranial focused ultrasound ablation (MRgFUS), which enable effective intervention while reducing the risk of complications.

At the same time, ongoing research in genetics and molecular therapies is contributing to the development of patient-specific treatment strategies. This creates an opportunity for the development of new, individually tailored therapies for people with drug-resistant epilepsy. [8,9]

1.2 Classic resection surgery in drug-resistant epilepsy

a) Resection of epileptic foci

Resection of epileptic foci involves the neurosurgical removal of trigger sites in the brain tissue where seizures are triggered. The use of innovative techniques can bring significant benefits to patients in reducing or completely eliminating drug-resistant epilepsy activity.

The latest scientific reports from April 2025, published in the systematic review “Stereotactic and Functional Epilepsy Surgery for Drug-Resistant Epilepsy in Africa: A Systematic Review” (Darko et al., 2025),

the most common surgeries performed to treat drug-resistant epilepsy were temporal lobectomy (59.6%) and lesionectomy (9.6%). After surgery, 80.6% of patients achieved Engel class I, which is equivalent to complete seizure freedom, while in long-term follow-up (1–5 years), 70.3% of patients maintained class I. Surgical complications occurred in 8.8% of patients [10].

Types of resection:

- **temporal lobectomy (ATL)**

Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy, in which lesions are most often located in the temporal lobe.

Anterior temporal lobectomy (ATL) can effectively reduce the frequency and number of epileptic seizures in patients, with up to 60-70% of patients becoming seizure-free 1-2 years after surgery. Approximately 50% of patients remain seizure-free for up to 10 years [11].

Surgical methods used in the treatment of temporal lobe epilepsy (DRE) can be classified as open or minimally invasive. Temporal lobectomy accounts for approximately half of all specialized procedures aimed at treating drug-resistant epilepsy. A prospective, randomized controlled trial showed that ATL, along with removal of structures of the medial temporal lobe, was more effective than pharmacotherapy in cases of drug-resistant epilepsy and DRE. A meta-analysis of data from 22 studies on the effect of ATL on DRE allowed for the evaluation of results in different observation time intervals, divided into three groups: 12–24 months, 24–48 months, and ≥48 months. In the entire group, 62% of patients had no seizures after surgery (95% CI: 45%–79%). In the group observed for 12–24 months, 71% of patients remained seizure-free (95% CI: 60%–82%), while in the 24–48 month interval, this figure was 61% (95% CI: 50%–71%), However, in the observation lasting ≥48 months, 53% of patients achieved seizure freedom (95% CI: 25%–82%). [11].

Standard anterior temporal lobectomy (ATL) requires the removal of 4-6 cm of the anterior temporal lobe, as well as structures of the middle temporal lobe: the amygdala, hippocampus, uncus, temporal part of the piriform cortex, along with removal of the temporal and lateral parts (insular region) to ensure adequate access and eliminate the epileptogenic zone. This procedure is mainly recommended for adults. [7,12].

- **selective amygdalohippocampectomy (SelAH)**

Selective amygdalohippocampectomy (SelAH) is used in patients with epilepsy whose epileptogenic focus is located in the temporal lobe. It is an alternative to temporal lobe lobectomy (ATL), and this technique can be used in patients with drug-resistant temporal lobe epilepsy. Before performing the SelAH procedure itself, the patient must be properly qualified using neuroimaging, clinical, and neurophysiological tests to determine the source of epileptic activity. Magnetic resonance imaging (MRI) can reveal changes in the temporal structures, most commonly in the form of hippocampal atrophy, often accompanied by hyperintensity of T2-weighted and FLAIR signals. [13].

The goal of surgical treatment of epilepsy is adequate seizure control while limiting the risk of postoperative complications, such as neurological and cognitive deficits, for which preoperative diagnosis of the epileptogenic focus is extremely helpful. This significantly reduces the incidence of postoperative complications and increases the success rate of neurosurgical procedures. [14].

One such procedure is selective amygdalohippocampectomy (SelAH), which involves the precise removal of small fragments of the amygdala and hippocampus in the temporal lobe. Using neuronavigation, we can plan the craniotomy accordingly, with prior dissection of the skin and temporal fascia. After opening the dura mater, the incision site is marked, usually 2.5-3 cm posterior to the temporal pole. Next, dissection is performed towards the temporal horn until it is opened, two retractors are inserted to expose the surgical field, and the parahippocampal gyrus is removed, starting with the removal of the uncus. Using neuronavigation, dissection is continued posteriorly, removing the anterior part of the uncus in the next step. After this resection, a characteristic indentation is revealed, in which elements of the internal carotid artery and oculomotor nerve can be seen. The next step is to mobilize the hippocampus laterally and gradually resect it posteriorly until the level of the cover plate is reached. Next, the soft meninges of the brain stem and the anterior choroidal artery are exposed, the completeness of the resection is assessed, and hemostasis is achieved. In this way, selective amygdalohippocampectomy has become an alternative to anterior lobectomy in patients with drug-resistant epilepsy. [13].

Other surgical approaches:

1. Lateral transcortical selective amygdalohippocampectomy

The patient is placed in a supine position, with the head turned in the opposite direction to the lobe being operated on and tilted downward. Selective resection of the amygdala and hippocampus is performed, usually

from the anterior to the posterior part, while preserving important vascular and neural structures. With this technique, most of the epileptogenic tissue can be removed with little or no vascular manipulation. [15].

2. Selective subtemporal amygdalohippocampectomy

The patient should be placed under general anesthesia. Subtemporal access requires adequate relaxation of the brain by means of hyperventilation, hyperosmosis, or PMR drainage from the lumbar region. The head should be rotated 90 degrees to move the temporal lobe away from the bottom of the middle fossa. Using this method, it is possible to preserve the temporal stem, white matter tracts, and pathways involved in language function. [15].

3. Pterional transsylvian selective amygdalohippocampectomy

It is necessary to open the Sylvian fissure widely in order to safely reach the structures of the medial temporal lobe. The Sylvian veins on the sides of the temporal lobe should be dissected, and during the procedure, the amygdala and the anterior part of the hippocampus are removed, while preserving the remaining part of the temporal lobe. [15].

4. Selective amygdalohippocampectomy via paramedial supratentorial-prenostal access.

The patient is placed in a semi-sitting position with the torso raised at a 20-degree angle (to reduce the risk of air embolism). A paramedial craniotomy is performed, the dura mater is incised, and access to the lower part of the brain is gained. The PMR is released, the cerebellar tentorium is coagulated, and resection of the posterior part of the hippocampus, the parahippocampal gyrus of the amygdala, and the uncus is performed, preserving the main vascular structures [16].

Temporal lobe epilepsy (TLE) is one of the most common syndromes involving focal seizures. Its mesial form may be associated with hippocampal sclerosis (HS), while showing resistance to pharmacological treatment of epilepsy and opening up possibilities for surgical treatment methods such as temporal lobectomy (ATL) or selective amygdalohippocampectomy (SelAH) [14].

b) Differences between temporal lobectomy (ATL) and selective amygdalohippocampectomy (SeIAH)

A study conducted in 2025 using a modified Delphi method with anonymous questionnaires demonstrated a link between complications associated with anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (selAH) in children and adults. The questionnaires were sent to surgeons from 37 different centers, 43% of whom responded, resulting in 39 responses.

The following complications were taken into account:

1. Mortality: This question was answered by 39 panelists in the context of ATL in children, 28 in the context of selAH in children, 36 in the context of ATL in adults, and 30 in the context of selAH in adults. All surgeons agreed that the mortality rate, regardless of age and surgical technique, ranged between 0% and 1%.

2. Visual field defects: Thirty-eight panelists participated in answering questions related to this factor for ATL in children, 28 panelists for selAH in children, 35 panelists for ATL in adults, and 29 panelists for selAH in adults. Regardless of the patient's age, the panelists agreed that the incidence of this type of complication was higher than 16% in patients who underwent ATL. In patients who underwent SelAH, a lower incidence of visual field defects was reported, with a frequency of less than 2% in children and approximately 5-10% in adults. Appropriate measures were recommended to reduce the incidence of visual field defects, including: appropriate surgical planning (use of probabilistic tractography - DTI Meyer loop), intraoperative monitoring (visual evoked potentials - VEP) and limited resection of the neocortex. The panelists agreed on the need to perform visual field testing both before and after surgery.

3. Motor deficits: In this case, 38 panelists participated, answering questions about ATL in children, 28 about selAH in children, 35 about ATL in adults, and 25 about selAH in adults. Most of the respondents stated that motor deficits, occurring with a frequency of 0-2% after ATL, are a rare phenomenon, and in patients after selAH, this rate was less than 2% in children and the same in adults. Attention was drawn to the need to take appropriate precautions to reduce the risk of permanent motor deficits using functional magnetic resonance imaging (fMRI), neuronavigation, or intraoperative neurophysiological monitoring using somatosensory evoked potentials (SSEP).

4. Infections: responses from 38 surgeons regarding ATL in children, 28 regarding selAH in children, 35 regarding ATL in adults, and 25 regarding selAH in adults were used. It was found that in all patients, the infection rate was approximately 2% in all patient groups. It was suggested that the incidence of the above-mentioned complication could be reduced by the use of preoperative antibiotics, primarily second-generation cephalosporins.

5. Postoperative hematomas: 38 panelists responded to this question regarding ATL in children, 28 regarding selAH in children, 35 regarding ATL in adults, and 25 regarding selAH in adults. In all groups of respondents, the incidence of postoperative hematomas was found to be less than 5%.

6. Psychiatric changes: 38 panelists participated in the case of ATL in children, 28 in the case of selAH in children, 35 in the case of ATL in adults, and 25 in the case of selAH in adults. In children, the incidence of psychiatric changes was less than 10%. In adults in both study groups, the respondents did not reach a consensus on the proportion for adults.

7. Cognitive deficits: The study was conducted with the participation of 38 panelists with ATL in children, 28 with selAH in children, 35 with ATL in adults, and 25 with SelAH in adults. No consensus was reached on the prevalence of this complication in any of the groups studied, but the majority of panelists reported cognitive deficits in individuals with selAH.

8. Language deficits: with the participation of 38 respondents with ATL in children, 28 with selAH in children, 35 with ATL in adults, and 25 with selAH in adults. This complication was considered rare in all study groups. The results ranged from 2% when both techniques were used in children to approximately 5% in adults when both surgical techniques were used[12].

Complications after ATL and selAH in children and adults
Complications after ATL and selAH in children and adults – panelist consensus

Table 1. Complications after ATL and selAH in children and adults – panelist consensus

Complication	Number of panelists (children ATL / children selAH / adults ATL / adults selAH)	Children – ATL	Children – selAH	Adults – ATL	Adults – selAH	Notes
Mortality	39 / 28 / 36 / 30	0–1%	0–1%	0–1%	0–1%	Full consensus regardless of age and surgical technique
Visual field deficits	38 / 28 / 35 / 29	>16%	<2%	>16%	5–10%	Recommended: surgical planning using Meyer's loop DTI tractography, intraoperative monitoring with visual evoked potentials (VEP), limited neocortical resection; visual field assessment before and after surgery
Motor deficits	38 / 28 / 35 / 25	0–2%	<2%	0–2%	<2%	Recommended: fMRI, neuronavigation, intraoperative somatosensory evoked potentials (SSEP) monitoring
Infections	38 / 28 / 35 / 25	~2%	~2%	~2%	~2%	Prophylaxis: preoperative antibiotic administration, primarily second-generation cephalosporins
Postoperative hematoma	38 / 28 / 35 / 25	<5%	<5%	<5%	<5%	No significant differences between groups
Psychiatric changes	38 / 28 / 35 / 25	<10%	<10%	No consensus	No consensus	Lack of agreement among panelists for adult patients
Cognitive deficits	38 / 28 / 35 / 25	No consensus	No consensus	No consensus	No consensus	Majority of panelists reported higher incidence after selAH
Language deficits	38 / 28 / 35 / 25	~2%	~2%	~5%	~5%	Rare complication in all study groups

- **frontal lobe resection**

Frontal lobectomy is the surgical removal of part of the frontal lobe where the epileptic focus is located. It is most commonly used in patients with drug-resistant frontal lobe epilepsy. If drug treatment fails, one of the ways to permanently or partially eliminate epileptic seizures in this area is frontal lobectomy.

In order for the procedure to proceed without complications, it is important to perform appropriate tests beforehand. These include preoperative EEG, MRI, and neuroimaging. Their purpose is to determine the approximate location of the epileptogenic part, in this case in the frontal lobe [17].

The operation itself should proceed without additional complications. In this case, it is important to remove the epileptic foci completely, or as much as possible, while preserving key structures, such as the language and motor areas [17, 18].

Craniotomy is the first stage of the procedure. After cutting through the skull and other structures surrounding the brain, direct access to the frontal lobe is obtained. Using neuronavigation and appropriate techniques, the surgeon attempts to remove the epileptogenic focus in accordance with anatomical and functional boundaries. One of the most important aspects is the proper preparation of structures in order to preserve the full functionality of the frontal lobe, which is mainly responsible for cognitive functions, planning, speech, and emotions [17].

Surgery can be performed using extensive frontal resection (eFL), i.e., removal of most of the lobe, including the orbital and parahippocampal gyri, while preserving the part of the lobe responsible for motor functions (FFL). Another option is functional frontal lobectomy, which uses mapping to allow for precise removal of the epileptogenic focus [17].

- **Risks and surgical complications**

Treatment of drug-resistant epilepsy using various surgical methods can be considered highly effective regardless of the treatment methods used. However, each method carries the possibility of side effects and complications. The risk, although quite low, is present in each of the cases mentioned and may occur at any stage of the surgical procedure.

Regardless of the technique, aspects such as mortality have been assessed as complications with a low or very low incidence rate.

In the case of temporal lobectomy (ATL), the most common complication is visual field defects, with motor and cognitive deficits (memory disorders) or psychiatric changes occurring less frequently.

Selective amygdalohippocampectomy (SelAH) is a less extensive operation than ATL, resulting in fewer complications. However, complications cannot be completely ruled out, with visual field disorders, motor disorders, and cognitive disorders being the most common.

Frontal resection is performed in patients with an epileptogenic focus located in the frontal lobe. The main risks involve speech disorders, motor function disorders, and behavioral changes. The extent of possible complications depends on the margin of the operated lesions and the possibility of their removal.

In summary, each of the above-mentioned methods of treating drug-resistant epilepsy has complications. Although they are not common, they still pose a risk to patients. Proper perioperative preparation is crucial, taking into account the patient's personal medical history, staff training, maintaining full concentration and sterility during the operation, while making use of the latest scientific reports and treatment methods.

1.3. Minimally invasive surgical methods

a) Laser thermotherapy of epileptic foci (LITT)

Minimally invasive surgical methods are currently becoming increasingly common in the treatment of drug-resistant epilepsy. These methods enable the precise removal or destruction of epileptic foci with as little damage to the surrounding brain tissue as possible. One of the most common minimally invasive surgical methods is laser thermotherapy of epileptic foci (LITT). This procedure involves the stereotactic insertion of a fiber optic catheter or probe into a designated area of the brain for selective thermal ablation, while monitoring heat distribution in real time using MR thermography. [19]

Thermography is an imaging method that detects infrared radiation emitted by various objects, including human body tissues. This phenomenon results in an image in the form of a thermogram, which is a graphical representation of the amount of infrared energy emitted or reflected by the tissue being examined. The image obtained by thermography shows the exact value and distribution of the temperature of the examined area of the body, which is closely correlated with the vascularization and metabolism of the analyzed tissue. [20]

Laser thermotherapy of epileptic foci has recently been gaining popularity as a minimally invasive alternative to the open surgical resection previously used in the treatment of drug-resistant epilepsy. LITT has

been shown to be effective in the treatment of drug-resistant epilepsy of various etiologies, including changes in the corpus callosum, cavernous malformations, focal cortical dysplasia, and epileptic tumors. [19] A meta-analysis of 43 studies and over 3,000 patients comparing minimally invasive surgical methods with open resection in the treatment of temporal lobe epilepsy (TLE) showed that 57% of patients undergoing laser interstitial thermal therapy (LITT) achieved Engel class I after surgery, while the same result was achieved in 69% of patients treated with anterior temporal lobectomy. Although the percentage of seizure-free patients remains higher with conventional open surgery, LITT is associated with fewer serious complications, including cognitive side effects. [19] Nevertheless, the available data on cognitive function after LITT are limited and heterogeneous. [21] Although LITT is particularly useful for treating hard-to-reach lesions, it has also demonstrated safety and efficacy in epileptic foci traditionally treated with open methods, such as temporal lobe epilepsy (TLE). Furthermore, patients undergoing laser thermotherapy experienced less pain compared to patients treated with conventional surgical methods. The length of hospital stay for patients treated with LITT was also reduced. [22]

b) Stereotactic radiosurgery (e.g., Gamma Knife)

Another minimally invasive surgical technique used in the treatment of drug-resistant epilepsy is stereotactic radiosurgery. Stereotactic radiosurgery (SRS), an example of which is Gamma Knife, involves the extremely precise delivery of a high dose of radiation, where the radiation beams are focused at a single point on the designated tissue, destroying it while precisely avoiding other areas. In the case of Gamma Knife, cobalt rays are used to deliver gamma radiation to a specific area of the brain without the need for conventional surgery.

In Gamma Knife technology, the patient's head is stabilized using a stereotactic frame, which virtually eliminates the possibility of movement and allows for very high irradiation precision, in the range of 0.2 mm–0.3 mm. Despite its suggestive name, as described above, this procedure does not involve the use of a knife or skin incisions.

Gamma Knife technology is used to treat epilepsy of various etiologies, including supratentorial tumors, hamartomatous tumors, cavernous malformations, and arteriovenous malformations. In the case of well-defined mesial temporal lobe epilepsy (MTLE), the clinical efficacy of Gamma Knife varies significantly, which is due, among other things, to differences in treatment protocols and irradiation techniques. Data indicate that higher doses directed at anatomical structures removed during classic open surgery produce better therapeutic results than lower doses or more limited irradiation areas. [23]

The history of Gamma Knife dates back to the end of the 20th century. The first use of stereotactic radiosurgery in the treatment of mesial temporal lobe epilepsy (MTLE) was described by Régis and colleagues as early as 1995 in a 25-year-old patient with long-standing partial complex seizures. [24] The patient received radiation directed at the amygdala and hippocampus, which led to complete remission of seizures during 16 months of follow-up, while continuing pharmacological treatment. Based on this experience, a larger study was conducted in 1999 involving 7 patients with treatment-resistant MTLE, using a similar dose and covering areas relevant to seizure generation (entorhinal cortex, hippocampus, amygdala). During an average follow-up of 34 months, 6 of the 7 patients achieved complete seizure remission (Engel IA). Side effects were minor and mainly included transient headaches and a single case of upper quadrantanopia. [25]

The postoperative course after stereotactic radiosurgery (RS) in patients diagnosed with medial temporal lobe epilepsy is similar to that observed after RS used in other neurological indications. However, clear changes in neuroimaging studies usually appear between 9 and 12 months after the completion of surgical treatment. Hyperintensity is most commonly observed in T2 sequences, probably reflecting the image of vascular edema, which increases after about 9 months and reaches its maximum after one year. It then gradually subsides over a period of 24–27 months. The mass effect caused by RS correlates temporally with the severity of T2-dependent changes. After their withdrawal, the remaining part of the temporal lobe often shows signs of moderate atrophy. The severity of these changes depends on the radiation dose, with higher doses leading to more pronounced effects. [26]

Changes in imaging studies are also accompanied by specific clinical manifestations reflecting the evolution of radiation damage. In the period after treatment, a temporary increase in the frequency of auras is often observed, followed by a gradual decrease in the number of epileptic seizures. In patients receiving higher doses of radiation, exacerbation

of symptoms, including auras and occasionally complex partial seizures, occurs earlier. Newly occurring headaches, which may precede changes visible in neuroimaging studies, are also an early clinical symptom. If

clinical improvement occurs, a reduction in seizure frequency usually occurs 12–18 months after RS and is related to the dose administered—higher doses promote faster seizure freedom.

Both the timing and severity of changes in brain imaging may be predictive of treatment efficacy. It has been shown that the volume of contrast enhancement and hyperintensity in T2 sequences on MRI performed 12 months after RS strongly correlates with subsequent seizure remission. Patients with a T2-dependent edema volume of less than 200 ml did not achieve seizure freedom during the 24–36 months of follow-up. Although this correlation is not fully predictive, the transient severity of auras is associated with the extent of T2-dependent edema and may be an indication for a follow-up MRI scan. [23]

In summary, numerous independent scientific reports confirm the efficacy and safety of Gamma Knife stereotactic radiosurgery in the treatment of drug-resistant medial temporal lobe epilepsy. In an analysis covering nine studies, complete seizure freedom within two years of surgery—often achieved earlier—was achieved in 46% of patients. In a subgroup of patients treated with higher doses of radiation, this percentage increased to as much as 58%. The frequency and nature of adverse events were comparable to those observed after resection amygdalohippocampectomy, with some studies showing that neuropsychological outcomes were better in patients undergoing Gamma Knife radiosurgery. However, the results obtained require further confirmation. Due to the large number of patients with temporal lobe epilepsy who are resistant to antiepileptic drugs and due to the morbidity associated with invasive open surgery, further research into non-invasive methods of radiosurgical treatment of epilepsy is of key importance. [23]

1.4 Neurostimulation in drug-resistant epilepsy

a) Vagus nerve stimulation (VNS) and responsive nerve stimulation (RNS)

Neuromodulation surgery techniques used in the treatment of drug-resistant epilepsy include vagus nerve stimulation (VNS) and responsive nerve stimulation (RNS). They have a similar mechanism of action but differ in their trigger areas. VNS is based on stimulation of the vagus nerve, while RNS is based on stimulation of reactive areas of the brain. The history of VNS dates back to 1990, when the technique was approved by the Food and Drug Administration (FDA) for the treatment of intractable epilepsy. By 2014, more than 100,000 patients had been treated with vagus nerve stimulation, with a therapy effectiveness rate of approximately 70%.

VNS is the technique of choice for children (e.g., with Dravet syndrome) and adults with a limited type of drug-resistant epilepsy who are not eligible for traditional surgical treatment.

The VNS procedure involves placing a stimulating electrode on the left vagus nerve in the left side of the neck, while the pulse generator is implanted in the chest area. During follow-up visits, the attending physician adjusts the stimulation parameters using a dedicated device and tailors them to the needs of the individual patient. Vagus nerve stimulation can have a beneficial effect on mood, consciousness, and memory in some patients, which translates into an improved quality of life for people with epilepsy. This method is currently considered safe and effective in both children and adults with focal and generalized drug-resistant epilepsy, and the number of patients eligible for this therapy is constantly growing. [27]

The mechanism of action of VNS involves activating a pulse generator at the onset of an epileptic seizure, which stimulates the vagus nerve, causing an increase in the amount of neurotransmitters released in the brain: norepinephrine and serotonin. The released neurotransmitters modulate the electrical activity of neurons and reduce the hypersynchronization of brain waves, which helps to reduce the excessive excitation associated with epileptic seizures. [28]

RNS for the treatment of drug-resistant epilepsy was approved by the Food and Drug Administration (FDA) in 2013. [29] The action of responsive nerve stimulation can be compared to that of a pacemaker—the system can monitor brain waves and respond to abnormal activity, especially that which causes seizures. Available scientific studies have shown that the use of RNS reduces the number of seizures and improves the quality of life for most patients. [30]

Electrodes in the form of small wires or cables are placed in one or two areas of the brain where seizure activity may occur. These wires are connected to a stimulator placed in the skull—the stimulator can release a series of impulses. (stimulation) to the brain when abnormal activity is detected. Such stimulation can stop epileptogenic activity even before the onset of an epileptic seizure. The advantages of RNS include no need for precise localization of the epileptic focus, less trauma leading to fewer side effects, procedure effectiveness of up to 70%, and association with improved mental, emotional, and cognitive function and quality of life in most patients. Indications for VNS and RNS treatment include a diagnosis of inoperable multifocal epilepsy, unclear epileptic location after thorough preoperative clinical evaluation, recurrent seizures after surgery, total and partial epilepsy of unknown cause, and a group of patients who do not consent to surgery using conventional methods. [27]

b) Deep brain stimulation

Deep brain stimulation (DBS) is a neuromodulatory therapy involving the surgical implantation of electrodes into deep brain structures to modulate and normalize brain activity in various neurological disorders. The mechanisms of DBS function at the micro, meso, and macroscopic levels, affecting neuronal signaling, synaptic reorganization, and network connectivity between brain areas [31].

In modulation surgery, the DBS device is implanted in a precisely defined location in the brain, where thin electrodes transmit electrical impulses from a battery-powered nerve stimulator [32]. This system can be programmed similarly to a pacemaker, allowing the stimulation parameters to be adjusted to the needs of a specific patient. Unlike the uncontrolled conduction of pathological impulses, which is assumed to occur in epilepsy, DBS generates artificial current in fixed cycles, which allows specific neural circuits to be blocked or modulated, thereby preventing epileptic seizures or reducing their frequency [33].

In 2018, the US Food and Drug Administration (FDA) approved anterior thalamic DBS (ANT-DBS) for the treatment of patients with drug-resistant focal epilepsy in whom surgical treatment or other less invasive neuromodulation methods have proven impossible or ineffective. DBS is currently indicated for the treatment of selected forms of epilepsy, particularly drug-resistant focal epilepsy. Qualification for DBS requires a detailed preoperative clinical evaluation of the patient, including seizure type, epileptic focus location, surgical risk, and potential therapeutic benefits. In cases where resection of the epileptic focus is not possible, neuromodulation devices such as RNS, VNS, or DBS may be considered.

Currently, the most commonly used method of implanting DBS electrodes in the anterior thalamic nucleus (ANT) is direct neurosurgery, in which the mammillothalamic tract (MTT) is an important landmark [34].

Data from the use of DBS in the treatment of dyskinesia emphasize the appropriate selection of patients and precise electrode placement as key factors influencing clinical outcomes, as well as their importance in the treatment of epilepsy. It is suggested that DBS stimulation sites should be selected according to individual patient characteristics, including seizure location. The results of the SANTE (Stimulation of the Anterior Nucleus of the Thalamus in the Treatment of Epilepsy) study showed that DBS electrodes do not always have to be placed directly within the ANT, as effective stimulation can also be achieved through contacts located outside the nucleus. Therefore, the optimal stimulation site remains the subject of further research [35].

The results of the SANTE study also showed that bilateral thalamic stimulation is a safe surgical procedure in patients with drug-resistant focal epilepsy. This therapy leads to a reduction in seizure frequency in both the short and long term and to a significant improvement in patients' quality of life. The results of previous studies were confirmed in subsequent cohort studies, in which the average percentage of patients responding to treatment was approximately 50% after one year of ANT-DBS. It should be emphasized that the degree of seizure control varies greatly from person to person, and the beneficial effects of DBS may become apparent gradually. As with other neuromodulation methods, it takes time to achieve the full therapeutic benefits of DBS.

DBS therapy is usually used to support pharmacological treatment, and if patients show gradual improvement in seizure control, it is possible to reduce the doses of antiepileptic drugs. [36]

In summary, both surgical resection and alternative methods of neural modulation, including DBS, are promising strategies for the treatment of drug-resistant epilepsy.

2. Methodology

This review is based on current literature available in PubMed, Scopus, and Google Scholar databases, with particular emphasis on the latest systematic reviews and meta-analyses concerning modern surgical strategies in the treatment of drug-resistant epilepsy. The analysis covered resection of epileptic foci, minimally invasive procedures, and neurostimulation. The review included results concerning seizure reduction, surgical complications after procedures, and the quality of life of patients after surgery. The literature search was conducted using keywords such as: drug-resistant epilepsy, epilepsy surgery, focal resection, seizure control, innovative therapies.

3. Results

The reviewed literature demonstrates that surgical treatment significantly improves seizure control in patients with drug-resistant epilepsy compared with continued pharmacotherapy. Resective procedures, particularly anterior temporal lobectomy and selective amygdalohippocampectomy, were associated with the highest rates of long-term seizure freedom. Minimally invasive techniques, including laser interstitial thermal therapy and stereotactic radiosurgery, achieved slightly lower seizure-free rates but showed a favorable safety profile, reduced cognitive morbidity, and shorter hospitalization times. Neuromodulation strategies such as vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation consistently resulted in meaningful seizure reduction and improvements in quality of life, although complete seizure remission was less frequent. Reported complication rates across all surgical modalities were generally low.

4. Discussion

These findings highlight the pivotal role of surgical and neuromodulatory interventions in the management of drug-resistant epilepsy. While open resective surgery remains the most effective approach for achieving seizure freedom, minimally invasive procedures offer an important alternative for patients with lesions in eloquent brain regions or increased surgical risk. Neuromodulation expands treatment options for individuals with multifocal or non-localizable epileptogenic zones. Variability in study design, outcome measures, and follow-up duration across studies limits direct comparisons and underscores the need for standardized assessment frameworks.

5. Conclusions

Modern surgical and neuromodulatory therapies constitute effective treatment options for drug-resistant epilepsy, significantly improving seizure outcomes and patient quality of life. Advances in neuroimaging, stereotactic techniques, and stimulation technologies have enabled more individualized and safer treatment strategies. Future research should focus on long-term comparative studies, refinement of patient selection criteria, and further development of minimally invasive and adaptive neuromodulation approaches.

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