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PROSPECTS FOR THE USE OF DEEP BRAIN STIMULATION IN THE TREATMENT OF PARKINSON'S DISEASE IN UKRAINE

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Key words: *Parkinson's disease, deep brain stimulation, radiofrequency destruction*
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Abstract. Prospects for the use of deep brain stimulation in the treatment of Parkinson's disease in Ukraine. Kostiuk K.R., Lisianyi A.O., Medvediev Yu.M., Popov A.O., Cheburakhin V.V., Buniakin V.M., Tevzadze D.A. *Aim of the study – evaluation of the results of various methods of surgical treatment of Parkinson's disease depending on the clinical manifestations and stage of the disease. The study included 566 patients with Parkinson's disease (PD), comprising 201 (35.5%) women and 365 (64.5%) men, aged 30 to 79 years (mean age 52.9±8.8 years). Radiofrequency (RF) destruction of the subcortical nuclei was performed on 522 patients: 392 underwent unilateral thalamotomy, 50 underwent bilateral thalamotomy, 36 underwent unilateral pallidotomy, 2 underwent bilateral pallidotomy, 30 underwent thalamotomy combined with contralateral pallidotomy, and 12 underwent thalamotomy combined with contralateral subthalamic nucleus destruction. Additionally, neurostimulation surgery was performed on 37 patients, and combined surgical interventions (stereotactic RF destruction and deep brain stimulation (DBS) system implantation) were performed on 7 patients. Postoperative follow-up ranged from 1 to 16 years (mean follow-up 5.2±0.9 years). One year after RF unilateral thalamotomy, tremor abolishing or significant regression was observed in 374 out of 392 patients (95.4%). Rigidity regressed in 278 out of 314 patients (88.5%) who had it before operation. Postoperative complications from unilateral thalamotomy occurred in 18 patients (4.6%). Following staged bilateral thalamotomy, tremor regression was observed in 48 out of 50 patients (96.0%) and motor fluctuations regressed in 15 out of 28 patients (53.6%). The rate of surgical complications was higher after bilateral thalamotomy (8.0%) compared to unilateral thalamotomy. After unilateral and staged bilateral pallidotomy, tremor and rigidity regression were achieved in more than two-thirds of operated patients, and levodopa-induced dyskinesias stopped in over 80% of cases. The best outcomes for alleviating motor symptoms were observed in patients who underwent DBS treatment. Staged bilateral RF ablation can be considered an alternative surgical treatment for a highly selected group of patients.*

Реферат. Перспективи застосування глибинної стимуляції мозку в лікуванні хвороби Паркінсона в Україні. Костюк К.Р., Лісяний А.О., Медведєв Ю.М., Попов А.О., Чебурахін В.В., Бунякін В.М., Тевзадзе Д.А. *Мета роботи – оцінка результатів різних методів хірургічного лікування хвороби Паркінсона залежно від клінічних проявів та стадії захворювання. З 2008 до 2024 року було прооперовано 566 пацієнтів на хворобу Паркінсона. Серед них було 201 (35,5%) жінка та 365 (64,5%) чоловіків. Вік пацієнтів коливався від 30 до 79 (у середньому 52,9±8,8 року). Радіочастотна (РЧ) деструкція підкіркових ядер проведена 522 хворим. Серед них однобічна таламотомія – 392, двобічна таламотомія – 50, однобічна палідотомія – 36, двобічна палідотомія – 2, таламотомія та контрлатеральна палідотомія – 30, таламотомія та контрлатеральна деструкція субталамічного ядра – 12. Нейростимулювальна операція проведена 37 хворим. Комбіновані хірургічні втручання, а саме стереотаксична РЧ деструкція та імплантація системи для глибинної стимуляції мозку (ГСМ), проведені 7 хворим. Післяопераційний катамнез простежено в термін від 1 до 16 років (у середньому 5,2±0,9 року). Через 1 рік після РЧ однобічної таламотомії припинення або значний регрес тремору відзначались у 374 з 392 (95,4%) хворих. Нормалізація м'язового тонусу спостерігалась у 278 (88,5%) із 314 хворих, у яких ригідність була до операції. Постопераційні ускладнення однобічної таламотомії спостерігалися у 18 (4,6%) хворих. Після поетапної двобічної таламотомії регрес тремору відмічено в 48 (96,0%) з 50 хворих, а моторні флуктуації регресували в 15 (53,6%) з 28 хворих, у яких вони були до нейрохірургічного втручання. Відсоток операційних ускладнень був* *вищим порівняно з однобічною таламотомією і становив 8,0%. Однобічна та послідовна двобічна палідотомії призводили до регресу тремору в понад 2/3 оперованих хворих, регресу ригідності та леводопа-індукованих дискінезій у понад 80% спостереженнях. Найкращі результати щодо усунення моторних симптомів захворювання відмічені у хворих, яким була імплантована системи для ГСМ. Поетапна двобічна РЧ деструкція може бути запропонована як альтернативний метод хірургічного лікування чітко окресленій когорті пацієнтів.*

Parkinson's disease (PD) is a neurodegenerative disease that occurs as a result of the death of dopaminergic neurons of the substantia nigra [1, 2, 3]. The main motor symptoms of PD are bradykinesia, resting tremor, and rigidity. Further progression of the disease causes postural instability, impaired gait, balance, memory, mood, speech, and sleep disorders [4, 5]. According to the literature, about 2% of the world's population over 65 years old suffer from PD [6]. The prevalence of this disease is on an average 150 cases per 100,000 population, and the annual incidence varies from 5 to 20 cases per 100,000 population [7]. At the same time, the incidence of PD in Ukraine is only 60 cases per 100,000 population, which may indicate a significant number of undetected cases [8]. At present, the etiological factors of PD remain incompletely elucidated. To date, there is no effectively proven therapy that could prevent the death of dopaminergic neurons. Medical and surgical treatment is aimed at reducing the severity of symptoms, slowing the progression of the disease and improving the quality of life of patients. The most common method of surgical treatment of PD was stereotaxic destruction of subcortical nuclei – ventrolateral nuclei of the thalamus and the internal segment of the globus pallidum [9, 10]. Currently, the priority direction is chronic electrical stimulation of the deep structures of the brain, which leads to a significant regression of movement disorders and improves the quality of life of patients [11]. The modern era of neurostimulation was started by A. Benabid, who in 1987 introduced the use of high-frequency deep brain stimulation (DBS) in the treatment of tremor in PD [1, 13]. Based on the results of a multicenter clinical study published in 2001, the US Food and Drug Administration (FDA) approved the use of DBS for the treatment of PD [14]. In Ukraine, for the first time the implantation of the system for the DBS was carried out at the State Institution “Romodanov Neurosurgery Institute” National Academy of Medical Sciences of Ukraine" in 2012 [15, 16]. The subthalamic nuclei (STN) (Fig. 1) and the internal segment of the globus pallidus internus (GPi) are the main targets of neurostimulation in the treatment of PD [17]. The purpose of the work is to evaluate the results of various methods of surgical treatment of Parkinson's disease depending on the clinical manifestations and stage of the disease.

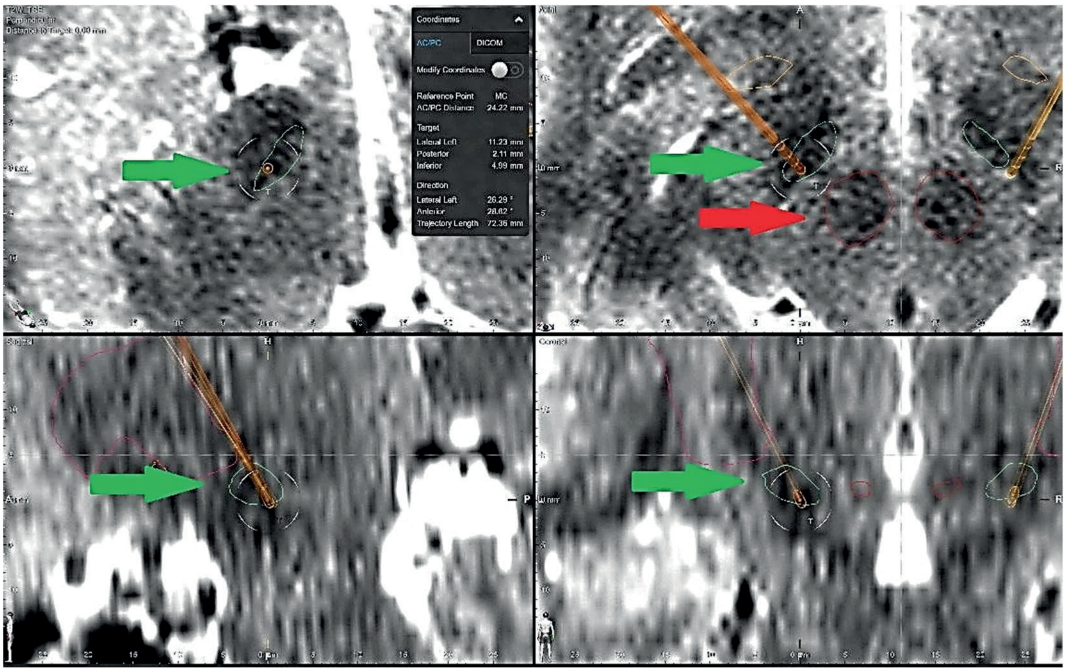

Fig.1. Calculation of the electrode implantation target for STN stimulation at the ELEMENT planning station (Brainlab), green arrow – STN, red arrow – nucleus ruber.
A – orthogonal; B - axial; C – sagittal; D - coronal projection

MATERIALS AND METHODS OF RESEARCH

From 2008 to 2024, 566 PD patients were operated on in the Department of Functional Neurosurgery and Neurostimulation. Among them there were 201 (35.5%) women and 365 (64.5%) men. The age of the patients ranged from 30 to 79 (52.9±8.8 years on average). Indications for surgical intervention were the progressive course of the disease, the ineffectiveness or low effectiveness of specific antiparkinsonian therapy, the development of side effects from the long-term use of antiparkinsonian drugs in the form of motor fluctuations (MF) and levodopa-induced dyskinesias (LID). Thus, regardless of the age of the patients and the duration of the disease, surgical treatment was carried out in the late stages of the disease. Dominant symptoms in the course of the disease played a key role in choosing the target of surgical treatment. The high cost and limitations of state funding were obstacles to the use of DBS in potential candidates for system implantation.

RF destruction of subcortical nuclei was performed in 522 patients. Among them: unilateral thalamotomy – 392, bilateral thalamotomy – 50, unilateral pallidotomy – 36, bilateral pallidotomy – 2, thalamotomy and contralateral pallidotomy – 30, thalamotomy and contralateral STN destruction – 12. Neurostimulating surgery was performed on 37 patients. Combined surgical interventions, namely stereotaxic RF destruction and implantation of a system for deep brain stimulation, were performed in 7 patients (Table 1).

Table 1

Distribution of patients depending on type of neurosurgical intervention

Surgeries	Number, (%)
RF unilateral thalamotomy	392 (69.25%)
RF bilateral thalamotomy	50 (8,83%)
RF unilateral pallidotomy	36 (6,36%)
RF bilateral pallidotomy	2 (0,35%)
RF thalamotomy and contralateral pallidotomy	30 (5,30 %)
RF thalamotomy and contralateral STN destruction	12 (2,12%)
DBS	37 (6,53%)
RF unilateral thalamotomy and following DBS	7 (1,23%)
Total	566 (100%)

Stereotaxic interventions were performed on a CRW Radionics stereotaxic system (Radionics Inc.). Calculations of the coordinates of the destruction target and the neurostimulating electrode insertion target were performed on planning stations StereoFusion, StereoPlan, Atlas (Radionics Inc), Fraimlink, StealStation (Medtronic), iPlan and ELEMENT (Brainlab).

An indirect method was used to calculate the coordinates of the ventrolateral nuclei of the thalamus (mainly the intermediate ventrolateral nucleus – Vim), since these nuclei cannot be visible on modern magnetic resonance imaging (MRI) images. The intercommissural line (AC-PC line), which connects the anterior and posterior commissures, is the basis for indirect calculation of the target coordinates of stereotaxic destruction or intracerebral electrode implantation. According to the AC-PC line, the coordinates of the subcortical structures of all modern stereotaxic electronic atlases are calculated. Modern technologies make it possible to use tracts to determine the optimal place for RF destruction or implantation of electrodes for DBS (Fig. 2) [18].

The calculation of the coordinates of the globus pallidus and subthalamic nucleus (STN) was carried out by the "direct" method, since the technical capabilities of modern MRI machines provide the opportunity to determine not only the localization of the above-mentioned structures with sufficient accuracy, but also to detail their individual segments on MRI images. The targets of stereotaxic intervention were the posterior-ventro-lateral part of the internal segment of the globus pallidus (GPi) and the dorsolateral area of the sensorimotor zone of the STN. It should be noted that the coordinates of the STN target for ablation were slightly higher compared to the STN target for intracerebral electrodes intended for DBS. Table 2 presents the coordinates of the targets of stereotaxic interventions.

All operations were performed under "wake-up" anesthesia, in order to intraoperatively assess the regression of motor manifestations of PD and prevent the development of neurological complications associated with incorrect placement of electrodes [19]. In all cases, test macrostimulation with a frequency of 75-100 Hz was performed, with a gradual increase in amplitude from 0 to 2.0 Volts, during which the regression of motor disorders, namely tremor and rigidity, was assessed. After that, low-frequency (2 Hz) test macrostimulation with a gradual increase in amplitude from 0 to 3.5 Volts was performed.

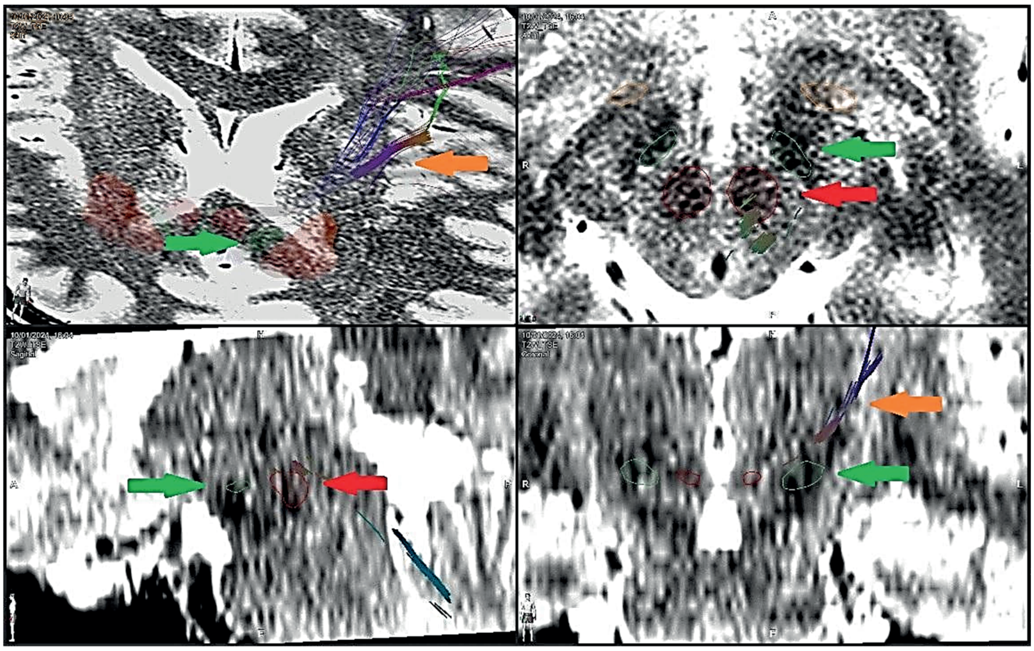

Fig. 2. Calculation of the location of the dentatorurobrothalamic tract (DRTT) (orange arrow) relative to the STN (green arrow) and Nucleus ruber (red arrow).
A – orthogonal; B – axial; C – sagittal; D – coronal projection

This type of intraoperative macrostimulation made it possible to determine motor response thresholds to test stimulation [20]. In the absence of regression of the motor manifestations of PD or the appearance of pathological neurological signs, namely spastic contraction of the limbs, the electrode was removed and the place of its re-implantation was corrected, depending on the response to the test stimulation. According to the results of the test macrostimulation, the need for the electrode re-implantation occurred in 8% of patients who were subsequently subjected to RF destruction of the subcortical nuclei.

Table 2

Mean coordinates of targets of stereotaxic surgery

Target of stereotaxic intervention	Coordinates relative to the central point of the intercommissural line (AC-PC)		
	laterality - (x)	antero-posterior direction (y)	verticality (z)
Vim	13,6	- 4,8 2	0
GPi	21,5	+ 2,8	- 3,7
STN for ablation	11,8	- 2,5	- 4,6
STN for neurotimulation	11,9	- 2,3	- 5,2

Implantation of the system for DBS was carried out using a conventional technique. During surgery, intracerebral electrodes were implanted in the anterior subclavian structures, a pulse neurogenerator was implanted at the infracerebral space of the breasts in the subclavian subclavian area and with the help of special footwear, which were carried out under the skin, connecting with electrodes [21].

Intraoperative test microstimulation was performed during implantation of electrodes for DBS in 8 (20.0%) patients. Microelectrorecording made it possible to determine the most correct place of implantation of intracerebral electrodes, based on the fixation of specific electrical activity of various functional zones of subcortical nuclei.

Immediately after implantation of intracerebral electrodes, patients underwent multispiral computed tomography to determine the correctness of electrode location. Modern software makes it possible to clearly determine the location of electrodes according to a previously developed plan, relative to brain structures and tracts involved in the pathogenesis of the disease (Fig. 3, 4).

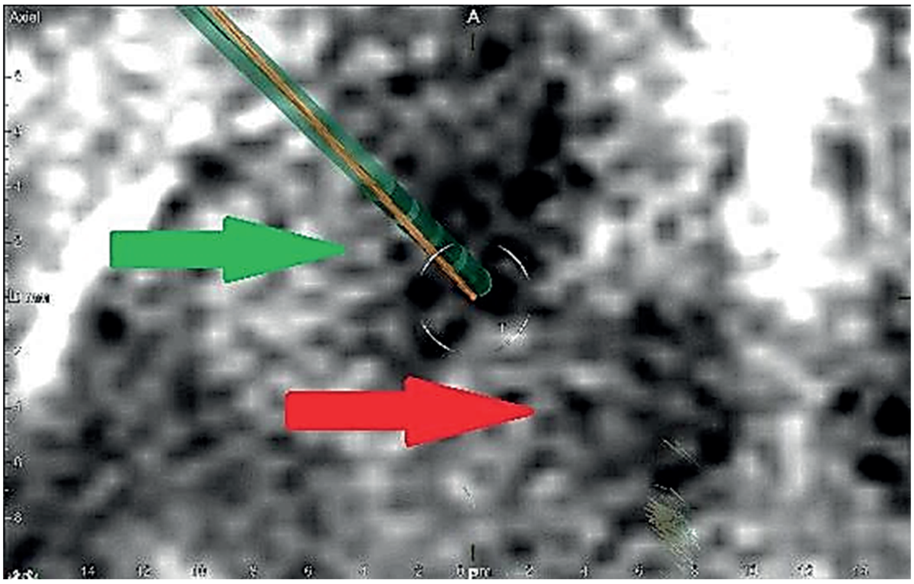

Fig. 3. Comparison of electrode location (green) in the STN nucleus with the planned trajectory (orange), STN (green arrow) and Nucleus ruber (red arrow). A – axial projection

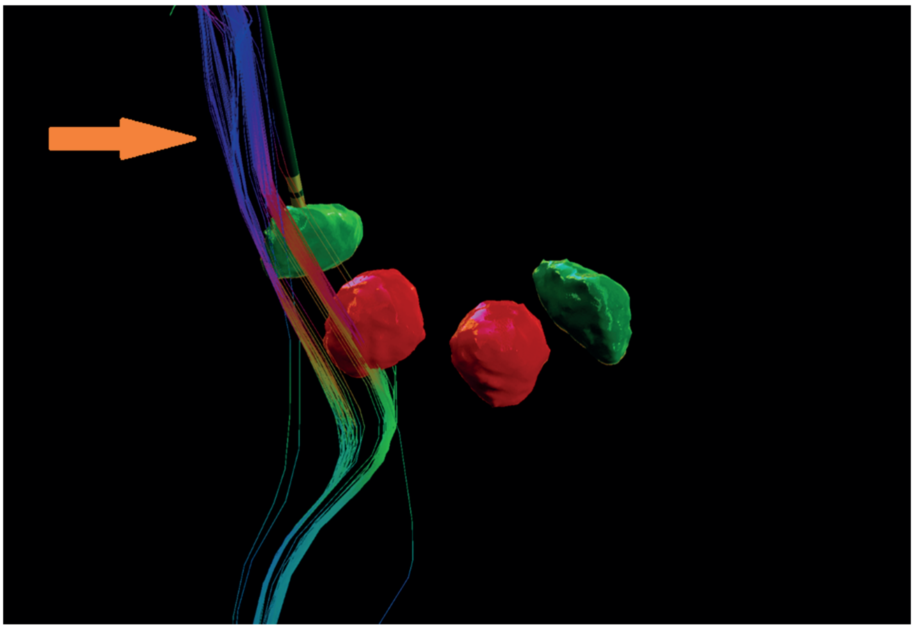

Fig. 4. Electrode location relative to the dentatorubrothalamic tract (orange arrow) according to postoperative control data (STN highlighted in green, Nucleus Ruber highlighted in red, DRTT – orange arrow). Oblique coronary projection

The state of the patients, the nature of the course of the disease and the dynamics of the neurological status after the operation were evaluated according to the generally accepted Unified Parkinson's Disease Scale (UPDRS), the Hoehn and Yahr Rating Scale, the shortened mini-mental state examination (MMSE) scale, and the Schwab and England Activities of daily living scale (MSEADL) [22, 23, 24, 25].

The postoperative catamnesis was traced in the period from 1 to 16 years (on average 5.2±0.9 years). The neurological status of the vast majority of patients was assessed 1 and 2 years after neuro-surgical intervention, respectively – in 540 (95.4%) and 412 (72.8%) observations. Control examination of patients who underwent DBS was carried out 1 and 2 years after the operation in 38 (95.0%) and 36 (90.0%) of 40 patients, respectively. The high rate of post-operative examination of patients who underwent DBS is due to the need for more frequent patient visits to correct neurostimulation parameters.

The studies were carried out within the framework of the scientific research work UDC 616.858:616.89-089.12 "To study the peculiarities of mental disorders in patients with Parkinson's disease and to develop differentiated approaches to surgical treatment" in compliance with the main provisions of the "Rules of ethical principles of conducting scientific medical research with human participation", approved Declaration of Helsinki (1964-2013), ICH GCP (1996), EU Directive No. 609 (from 24.11.1986), orders of the Ministry of Health of Ukraine No. 690 from 23.09.2009, No. 944 from 14.12.2009, No. 616 dated August 3, 2012, local protocols. The Ethics Committee of the State Institution "Romodanov Neurosurgery Institute" National Academy of Medical Sciences of Ukraine" detected no violations of ethical and moral and legal norms during the conduct of the research work (protocol No. 4 dated May 17, 2024). All patients signed an informed consent to participate in this study, and every precaution was taken to ensure their anonymity.

The data obtained as a result of clinical studies were subject to statistical processing. Traditional methods of parametric statistics were used to process the quantitative values of large volumes, which were subject to the normal distribution law, with the help of which the main parameters of the samples were determined, namely: the arithmetic mean, the error of the mean value, and the root mean square deviation. Equality of general variances was checked using Fisher's test. The test of the hypothesis regarding the equality of the general average values was carried out using the Student's t-test. The critical value of the statistical level was assumed equal to 0.05 (5%) [26].

Analysis and processing of statistical data after clinical studies was carried out on a personal computer using the IBM SPSS Statistics version 29 license No. 512186485 and MS Excel application programs.

RESULTS AND DISCUSSION

Stereotactic radiofrequency destruction was performed in cases of predominance of tremulous and rigid forms of PD or their combination. Unilateral and bilateral thalamotomy was performed in patients with tremor in the forefront in the clinical picture, while pallidotomy and DBS were performed in patients with akinetic-rigid or tremulous-akinetic-rigid forms of PD. The proportion of patients with akinetic-rigid and tremulous-akinetic-rigid forms of PD who underwent RF pallidotomy (unilateral or bilateral and in combination with contralateral thalamotomy) was significantly higher and made up 82.4%, compared to patients who underwent unilateral – or bilateral thalamotomy and thalamotomy in combination with contralateral subthalamotomy (total 11.0%), ($p<0.001$). In 38 out of 44 (86.4%) patients who underwent isolated DBS or in combination with unilateral RF thalamotomy, the symptoms of akinesia in combination with other motor disorders came to the fore. This indicator was slightly higher compared to patients who underwent pallidotomy, but there was no significant difference. At that time, tremor reliably prevailed in patients who underwent stereotaxic RF thalamotomy (Table 3).

Regardless of the type of surgical intervention, cessation or significant regression of tremors, normalization of muscle tone, correction of posture, increase in motor activity, and regression of levodopa-induced dyskinesias were observed in most operated patients. The best results were obtained after bilateral stimulation of the subthalamic nuclei.

One of the indications for pallidotomy was the presence and progression of LID, when destruction of the STN nucleus was performed in patients with MF, clinically manifested by the phenomena of "exhaustion" of the drug dose, "on-off", "sudden shutdown" or "death". In patients who had LID, destruction of the STN core was not performed, considering the high risk of developing hemiballism. While the presence of LID ("peak dose" dyskinesias, biphasic dyskinesias) was one of the main factors that determined indications for pallidotomy (unilateral or bilateral or combined thalamotomy with subsequent pallidotomy). The incidence of LID was significantly higher in patients who underwent various types of stereotaxic RF pallidotomy compared to those who underwent unilateral thalamotomy or thalamotomy and subsequent STN destruction, respectively 79.4% and 7.5% ($p<0.001$). While MF was more common in patients who underwent thalamotomy, this difference was not statistically significant when compared to those who underwent pallidotomy. In the vast majority of patients who underwent DBS, MF occurred, the proportion of which was higher but did not have a significant difference compared to patients who underwent thalamotomy. LID was also more common in patients who underwent DBS compared to those who underwent pallidotomy, but this difference was not significant (Table 4).

Table 3

Distribution of patients according to PD forms

Surgery	Form of Parkinson's disease				
	tremulous-rigid	tremulous	akinetic-rigid	tremulous akinetic-rigid	total
	abs. number, (%)	abs. number, (%)	abs. number, (%)	abs. number, (%)	abs. number, (%)
Thalamotomy unilateral	241 (61,5%)	103 (26,3%)	0 (0%)	48 (12,2%)^	392 (100%)
Thalamotomy bilateral	16 (32,0%)	32 (64,0%)*	0 (0%)	2 (4,0%)^	50 (100%)
Pallidotomy unilateral	6 (16,7%)	2 (5,6%)	12 (33,3%)*	16 (44,4%)	36 (100%)
Pallidotomy bilateral	0 (0%)	0 (0%)	1 (50,0%)	1 (50,0%)	2 (100%)
Thalamotomy + contralateral pallidotomy	4 (13,3%)	0 (0%)	11 (36,7%)*	15 (50,0%)	30 (100%)
Thalamotomy + contralateral destruction of STN	7 (58,3%)	5 (41,7%)*	0 (0%)	0 (0%)	12 (100%)
DBS	4 (10,8%)	0 (0%)	12 (32,4%)*	21 (56,8%)	37 (100%)
RF unilateral thalamotomy and following DBS	2 (28,6%)	0 (0%)	0 (0%)	5 (71,4%)	7 (100%)
Total	280 (49,4%)	142 (25,1%)	36 (6,4%)	108 (19,1%)	566 (100%)

Notes: significance of differences ($p<0.05$) of indicators when comparing groups: * – bilateral thalamotomy and thalamotomy + contralateral STN destruction with all other groups; # – pallidotomy is unilateral, thalamotomy + contralateral pallidotomy and DBS with all other groups; ^ – unilateral thalamotomy and bilateral thalamotomy with all other groups.

The best results in the elimination of motor symptoms of the disease were noted in patients with the implanted system for DBS. After such an operation, regression of tremor, rigidity and akinesia was observed in the vast majority of patients. In these patients, MF and LID partially regressed. The improvement of the patients' state was noted in the form of elimination or a significant reduction in the severity of the motor symptoms of the disease, which was reflected in the improvement of the UPDRS unified scale and the Schwab and England Activities of daily living scale. Similar results were also observed in patients with combined RF destruction and implantation of the DBS system (Fig. 5).

Table 4

Side effects of dopaminergic therapy

Surgery	Side effects of levadopa replacement therapy	
	MF	LID
	abs. number, (%)	abs. number, (%)
Thalamotomy unilateral (n=392)	195 (49,8%)	32 (8,2%)#
Thalamotomy bilateral (n=50)	28 (56,0%)	2 (4,0%)#
Pallidotomy unilateral (n=36)	14 (38,9%)*	32 (88,9%)
Pallidotomy bilateral (n=2)	0 (0%)	2 (100,0%)
Thalamotomy + contralateral pallidotomy (n=30)	20 (66,7%)	18 (60,0%)
Thalamotomy + contralateral destruction of STN (n=12)	12 (100 %)	0 (0%)
DBS (n=37)	34 (91,9%)	28 (75,7%)
RF unilateral thalamotomy and following DBS (n=7)	5 (71,4%)	4 (57,1%)
Total (n=566)	308 (54,4%)	118 (20,9%)

Notes: significance of differences ($p<0.05$) of indicators when comparing groups: * – unilateral pallidotomy with thalamotomy + contralateral destruction of STN, DBS, RF unilateral thalamotomy and subsequent DBS; # – unilateral thalamotomy and bilateral thalamotomy with unilateral pallidotomy, bilateral pallidotomy, thalamotomy + contralateral pallidotomy, DBS, RF unilateral thalamotomy and subsequent DBS.

Surgical complications occurred in 3 (6.9%) cases, 2 patients experienced hemorrhage at the site of implantation of intracerebral electrodes, which did not require neurosurgical intervention, in another patient local ischemia developed at the site of implantation of the electrode. In all three cases, the neurological deficit did not remain constant and regressed within 1-2 months. Complications directly related to neurostimulation were noted in 3 out of 44 (6.9%) cases.

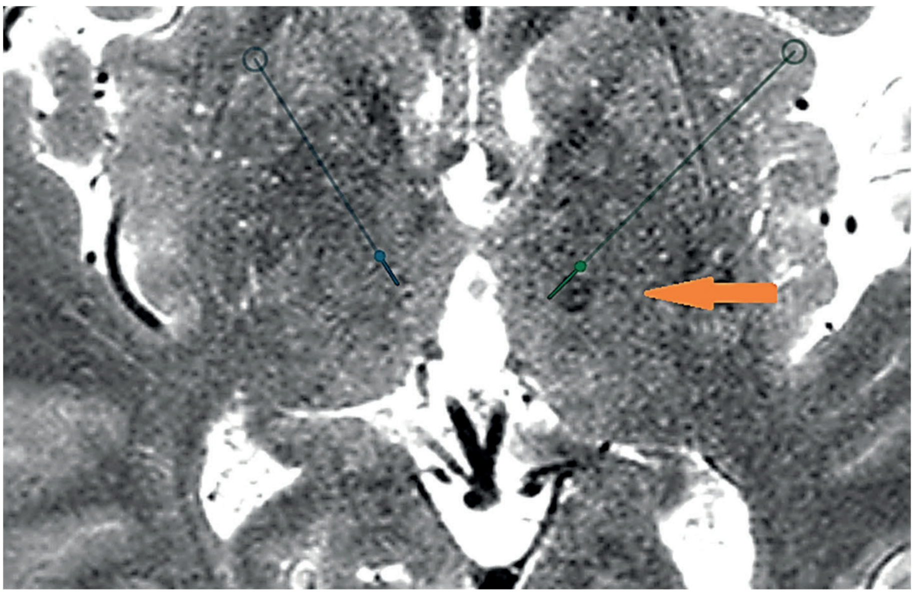

Fig. 5. Axial MRI projection of patient H., who underwent RF thalamotomy on the right (orange arrow); calculation of coordinates of STN nuclei for subsequent implantation of electrodes for bilateral neurostimulation

One patient developed severe depression one month after the start of neurostimulation, and required treatment in a psychiatric hospital. Two other patients had impulse control disorders. Incorrect implantation of intracerebral electrodes, which required their reimplantation, was noted in 2 (4.6%) cases. In another 1 (2.3%) observation, there was mechanical damage to the neurostimulating system (rupture of the extension cord), which required repeated surgery to replace it (Table 5).

Table 5

Results of surgical interventions

Type of surgery	Decrease of UPDRS scale scores, %		Increase of Schwab and England scale scores, %	Levodopa dose reduction, %	Surgical complications, n (%)	Mortality, n (%)
	State ON	State OFF				
Thalamotomy unilateral (n=392)	45,4%*	39.5%*	41,4%	29,3%*	18 (4,6%)	2 (0,5%)
Thalamotomy bilateral (n=50)	30,2%*	34,1%*	40,1%	32,4%*	4 (8,0%)	0 (0%)
Pallidotomy unilateral (n=36)	36,8%*	38,6%*	58,3%	17,2%*	1 (2,8%)	0 (0%)
Pallidotomy bilateral (n=2)	38,2%*	41,3%*	51,1%	21,1%*	0 (0%)	0 (0%)
Thalamotomy + contralateral pallidotomy (n=30)	33,0%*	38,9%*	36,2%	37,3%*	2 (6,7%)	0 (0%)
Thalamotomy + contralateral destruction of STN (n=12)	51,6%	44,8%	39,3%>	55,6%	0 (0%)	0 (0%)
DBS (n=37)	74,2%*	68,3%*	66,8%	52,4%*	2 (5,4%)	0 (0%)
Unilateral thalamotomy and following DBS (n=7)	67,5%	62,4%	59,8%	47,8%	1 (14,3%)	0 (0%)
Total (n=566)	47,3%	46,9%	49,1%	36,6%	28 (4,9%)	2 (0,4%)

Note. The difference is statistically significant ($p<0.05$) when comparing: * – indicators of DBS group with indicators of other groups.

After all types of stereotaxic interventions, a reliable regression of leading movement disorders was noted. Cessation of tremor was observed in 70.8-100% of operated patients (on average – 88.7%), regression of rigidity in 72.2-100% of observations (on average – 85.5%). Regression of akinesia was less pronounced and occurred in 34.6-80% of patients (48.3% on average). A statistically significant regression of akinesia was noted after unilateral and bilateral pallidotomy, as well as after neurostimulating operations, which led to the most pronounced positive effect in comparison with other stereotaxic interventions.

One year after RF unilateral thalamotomy, cessation or significant regression of tremor, as well as normalization of muscle tone, was noted in the vast majority of patients operated – 374 out of 392 (95.4%) patients. Recurrence of tremor was observed in the majority of patients the day after surgery, only in 4 (1.0%) observations recurrence of tremor occurred 2-3 months after neurosurgical intervention. Normalization of muscle tone was observed in 278 (88.5%) of 314 patients who had stiffness before surgery. After unilateral thalamotomy, complications were observed in 18 (4.6%) patients. In 7 (1.9%) cases, complications led to a permanent neurological deficit in the form of paresis of the contralateral upper limb, dysarthria, and sensitivity disorders in the contralateral limbs due to damage to the somatosensory ventrocaudal nucleus of the thalamus. In 9 observations, neurological disorders were transient and regressed within one week to 3 months after surgery. Two patients, aged 59 and 69, died as a result of massive hemorrhage at the site of destruction with blood breakthrough into the ventricular system. Thus, the mortality rate after unilateral thalamotomy was 0.5%. It should be noted that both deaths occurred in 2009 during the stages of implementation of the stereotaxic RF destruction method at the Institute.

After stepwise bilateral thalamotomy, regression of tremor was noted in 48 (96.0%) of 50 patients, and

MF regressed in 15 (53.6%) of 28 patients in whom they occurred before neurosurgery. The percentage of operative complications was higher in comparison with unilateral thalamotomy, being 8.0%. At the same time, permanent neurological deficit occurred in 2.7% of observations.

Unilateral and following bilateral pallidotomy led to regression of tremor in more than 2/3 of operated patients, regression of rigidity and LID – in more than 80% of observations. High control over MF was observed in patients who underwent DBS and bilateral RF destruction, in addition to bilateral thalamotomy (Table 6). While LID significantly regressed after implantation of the system for DBS and in patients who underwent RF pallidotomy in its different variations (Table 7).

Table 6

Regress of motor disorders depending on type of surgical intervention

Type of surgery	Tremor		Rigidity		Akinesia	
	before surgery, n	regress after surgery, n (%)	before surgery, n	regress after ssurgeryn, (%)	before surgery, n	regress after, n (%)
Thalamotomy unilateral (n=392)	392	375 (95,7%)	289	248 (85,8%)	48	19 (35,6%)
Thalamotomy bilateral (n=50)	50	48 (96,0%)	18	13 (72,2%)	2	0 (0%)
Pallidotomy unilateral (n=36)	24	17 (70,8%)	34	30 (88,2%)	16	9 (56,3%)
Pallidotomy bilateral (n=2)	0	0	2	2 (100%)	2	1 (50,0%)
Thalamotomy + contralateral pallidotomy (n=30)	19	14 (73,7%)	30	24 (80,0%)	26	9 (34,6%)
Thalamotomy + contralateral destruction of STN (n=12)	12	11 (91,7%)	5	5 (100%)	0	0
DBS (n=37)	25	24 (96,0%)	37	33 (89,2%)	21	16 (76,2%)*
Unilateral thalamotomy and following DBS (n=7)	7	7 (100%)	7	6 (85,7%)	5	4 (80,0%)*
Total (n=566)	529	469 (88,7%)	422	361 (85,5%)	120	58 (48,3%)

Note: significance of differences ($p<0.05$) of indicators when comparing groups: * – DBS, unilateral thalamotomy and subsequent DBS with all other groups.

DBS led to the cessation of MF in 80.0-91.2%, LID – in 75.0-92.9% of patients, which significantly improved the quality of life of patients. The regression indicators of MF and LID were reliably better compared to other types of operations. The high efficiency of neurostimulation can be explained by the careful selection of patients for neurosurgical intervention and the experience of surgeons.

Currently, in Ukraine, the majority of operations for the treatment of this disease are performed at the State Institution "Romodanov Neurosurgery Institute" National Academy of Medical Sciences of Ukraine", while both modern neurostimulating operations and classic RF destruction operations are performed. The first surgical interventions for the treatment of PD at the Kyiv Institute of Neurosurgery were carried out at the end of the 50s of the last century under the leadership of Professor O.O. Laponohov. He developed a stereotaxic apparatus of his own design, created a series of improved cryotomes for destruction of subcortical nuclei [12]. The newest era of surgical treatment of PD in Ukraine began in 2008, at the State Institution "Romodanov Neurosurgery Institute" National Academy of Medical Sciences of Ukraine" when with the participation of Professor Tipu Aziz of the University of Oxford (Great Britain) the first stereotaxic radiofrequency (RF) destruction of subcortical nuclei was performed using a planning station to determine the coordinates of the above-mentioned ablation targets.

Table 7

Regress of levodopa-induced motor disorders

Type of surgery	Motor fluctuations		Levodopa-induced dyskinesias	
	before surgery, n	regress after surgery, n (%)	before surgery, n	regress after surgery, n (%)
Thalamotomy unilateral (n=392)	195	118 (60,5%)	32	13 (40,6%)*
Thalamotomy bilateral (n=50)	28	15 (53,6%)*	2	0 (0%)*
Pallidotomy unilateral (n=36)	14	6 (42,9%)*	32	27 (84,4%)
Pallidotomy bilateral (n=2)	0	0 (0%)	2	2 (100%)
Thalamotomy + contralateral pallidotomy (n=30)	20	14 (70,0%)	18	14 (77,8%)
Thalamotomy + contralateral destruction of STN (n=12)	12	10 (83,2%)	0	0 (0%)
DBS (n=37)	34	31 (91,2%)*	28	26 (92,9%)*
Unilateral thalamotomy and following DBS (n=7)	5	4 (80,0%)	4	3 (75,0%)
Total (n=566)	308	198 (64,3%)	118	85 (72,0%)

Note: the difference is statistically significant ($p<0.05$) when comparing: * – indicators of the DBS group with indicators of other groups.

It should be noted that the vast majority of patients who underwent stereotaxic RF destruction of subcortical nuclei were candidates for implantation of a system for DBS. However, the limitation of budget funding significantly reduced the possibility of performing such operations. Despite this, RF destruction operations have demonstrated their high efficiency and safety.

Currently, bilateral destruction is not recommended due to the high risk of developing neurological complications. However, our results showed that asymmetric RF destruction, namely thalamotomy and contralateral pallidotomy or thalamotomy and contralateral destruction of the STN nucleus or bilateral pallidotomy can be effective and safe in a highly selective group of patients with bilateral PD. At the same time, unilateral thalamotomy is an effective method of eliminating tremor and rigidity in the lateralized form of PD. DBS should be offered to a clearly defined cohort of patients, taking into account the manifestations of PD, the presence of comorbidities and non-motor manifestations of the disease [27].

Modern studies indicate that individual, genetically determined forms of PD may respond differently to neurostimulation. It has been established that the LRRK2 p.G2019S, PRKN gene mutation is a prognostic factor for DBS, while the LRRK2 p.R1441G, LRRK2 p.T2031S and SNCA gene mutations may indicate a risk of rapidly progressive neurodegeneration and an unsatisfactory prognosis of neurostimulation.

The age of patients who are recommended to undergo surgical treatment remains debatable. According to the accepted standards, age older than 70-75 years is a contraindication for undergoing DBS, although modern studies show a tendency towards a significant expansion of age groups [3]. The vast majority of operated patients, namely 397 (70.1%) were aged from 50 to 70 years. 87 (15.4%) were under 50 years of age, another 70 (12.7%) patients were over 70 years of age. The age of the patients who underwent DBS ranged from 31 to 75 years (on average, 58.5 years).

Special attention needs to be paid to patients undergoing DBS in the advanced stages of PD. In such patients, despite neurostimulation, progressive resistance to dopaminergic therapy, the development of postural and cognitive impairments, which leads to a rapid decrease in the quality of life, is observed over time [28]. At the present time, the main criteria have been formed, according to which the expediency of DBS is determined for PD patients, the progressive course of the disease against the background of adequate therapy, which leads to a steady decrease in the quality of life, absence of significant mental and cognitive impairment (MMSE>22 scores; Beck depression scale <15 scores), as well as a stable and harmonious family and social status.

It should be noted that stimulation in some cases causes pronounced side effects. Many patients complain of dysarthric, dysphagic disorders, swallowing disorders, which can sometimes cause aspiration pneumonia. To prevent such complications, patients need careful preoperative screening for the presence of bulbar disorders [29]. Another disadvantage of DBS is the effect of neurostimulation on the emotional and cognitive functions of a person. In particular, long-term neurostimulation can negatively affect long-term memory, speech speed, and cause depression, anxiety, and impulse control disorders [30, 31, 32].

Studies of postoperative quality of life and emotional sphere after DBS contain conflicting data. DBSs have been associated with an increased risk of suicidal behavior in patients, although later controlled studies on the contrary indicate a reduced risk of suicide compared to patients on monopharmacotherapy. This necessitates a thorough preoperative examination of patients, multidisciplinary training of candidates for surgery together with neuropsychologists, screening of patients for anxiety and depression [33]. One of the most significant disadvantages of DBS is its high cost, which determines the need for a differentiated approach to the surgical treatment of PD. Last but not least, the experience of countries with a similar level of economic support for the population is useful for Ukraine [34, 35].

The above-mentioned problems and shortcomings of DBS determine the search for new solutions for the use of it. First, there is a need for a more sophisticated patient stratification system. M.C. Campbell et al. (2020) proposed dividing patients into cohorts depending on the available clinical picture: “only motor disorders”, “psychiatric and motor disorders”, “cognitive and motor disorders”. The distribution of patients according to such groups had high clinical accuracy and made it possible to clearly predict the expected quality of life, the progression of non-motor manifestations of PD (depression, apathy, social disorders) [36]. Second, the search for new neurostimulation targets that could provide the best clinical effect with minimal risk of complications in each individual case proceeds. Thus, stimulation of the pedunculopontine nucleus (PPN) is a potential target for improving gait and balance, stimulation of the posterior subthalamic area (PSA) is proposed as an alternative target for tremor control, and stimulation of the centromedian-parafascicular complex (9CM-Pf) may affect sensory perception, pain control, behavior and thinking. The Zona Incerta has been identified as the site of cross-connections of most of the basal ganglia and is currently considered an important target of DBS due to its effects on bradykinesia, tremor, and rigidity [37].

Constant updating of the technical support of the DBS continues, which allows to extend the duration of continuous operation of the battery, to focus the direction of stimulation and to minimize side effects. Completion of the final stage of the PROGRESS multicenter study established that the effectiveness of directional stimulation is practically no different from classical spherical neurostimulation, when directional neurostimulation reduces the risk of side effects compared to spherical stimulation [38, 39]. The significant energy consumption of traditional systems has led to the creation of closed-loop adaptive DBS management (aDBS) technology. Such systems are able to independently determine and control the necessary stimulation parameters according to the severity of motor disorders [40, 41]. Other potential directions of DBS include the development of reusable batteries with a total lifetime of up to 25 years, implants that allow reading and recording of deep electroencephalography and adjusting stimulation parameters, as well as the use of machine learning and functional MRI to determine the optimal target of DBS [42].

One of the most promising directions for the development of DBS is the technique of deep stimulation in the early stages of PD. A pilot prospective study by M. Hacker and co-authors (2021) on a cohort of patients at Hoen and Yahr stage 2 established that such early neurostimulation is associated with a lower dose of the necessary dopaminergic therapy than isolated pharmacotherapy, as a result of which the risk of side dyskinesias and motor fluctuations is reduced [43]. According to the meta-analysis conducted by P. Spindler and co-authors (2022), the early age of the patient and the shorter preoperative duration of "off" periods are significant prognostic factors of the positive effect of DBS [44].

It is also worth noting publications that observe a delay in the onset of late manifestations of PD, such as postural instability, bed rest, and mental disorders in patients after DBS compared to patients receiving pharmacotherapy. These studies require additional consideration [45].

In the end, instead of searching for a "gold standard", modern studies gravitate towards an individualized algorithm for the surgical treatment of PD. Treatment strategies include a combination of several modalities, including destructive procedures, intraintestinal levodopa pump “duodopa”, subcutaneous apomorphine infusions (CSAI), and MRI-guided ultrasound.

CONCLUSION

1. Deep brain stimulation is a reliable and safe method of surgical treatment that can significantly reduce the motor manifestations of Parkinson's disease.
2. Most of today's problems and discussions are significantly different from those that were at the beginning of the use of technology 20 years ago. The focus was on the possibilities of correcting non-motor symptoms, the impact of stimulation on the emotional sphere and quality of life of patients, expanding the cohort of potential candidates for stimulation.
3. New targets, combination of different types of surgical treatment, optimization of surgical interventions are discussed.
4. In Ukraine, the use of deep brain stimulation is becoming more and more widespread, however, compared to other countries, there is still an insufficient number of operations and timely application of generally recognized surgical treatment methods.
5. The reason for the limited use of the surgical method of treating Parkinson's disease lies not only in the limited state funding of high-cost technologies, but also in the insufficiency of a multidisciplinary approach to solving this problem. There should be a more in-depth collaboration between neurologists and neurosurgeons, based on an understanding of current capabilities, with a wider implementation of both ablative and neurostimulatory neurosurgical interventions.

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