Review article

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Modern surgical technologies management of malignant brain gliomas

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The authors presented the review of effective methods of preoperative multimodal neuroimaging, innovative navigation and laser technologies for targeted controlled resection of brain tumors. The issues of modern requirements for surgical treatment of malignant brain gliomas were considered. The advantages of clinical application of individualized treatment strategy to ensure the effectiveness of neurosurgical interventions in brain gliomas and prospects for further development of surgical technologies in neuro-oncology were also described.

Key words: *brain gliomas; treatment standards; neuronavigation; laser technologies; multimodal neuroimaging*

Surgical treatment of patients with brain tumors is an urgent problem of modern neuro-oncology. The incidence of brain tumors (both primary and metastatic) tends to steadily increase. The increase in the brain tumor morbidity rate is largely due to the influence of negative environmental factors. A certain role is also played by a social factor, namely the increase in life expectancy of the population (the probability of brain tumors increases in persons of older age groups), and clinical general availability of highly informative neuroimaging methods, which expanded the possibilities of early brain tumors diagnosis. The incidence of primary brain tumors is 12.8–14.0 cases per 100,000 population [1, 2]. Every year, up to 5,000 surgeries for malignant and benign brain tumors are performed in specialized neurosurgical clinics of Ukraine.

Glial tumors of various degrees of malignancy account for 40–45% of primary brain tumors. The largest group of glial tumors is grade III and IV tumors, glioblastomas (45–50%) and anaplastic gliomas (15–20%) [1, 2].

Glial tumors are characterized by infiltrative growth, which, taking into account their spread into functionally significant areas of the brain and median structures, limits the possibilities of traditional neurosurgery for performing radical surgeries and requires the development and clinical introduction of fundamentally new highly effective technological processes of surgical interventions.

Surgical treatment of brain tumors as the main stage of treatment involves the maximum possible resection of tumor tissue within functionally reasonable limits. Tumor cytoreduction ensures effective internal decompression, provides material for accurate histological verification of the tumor, and also provides time reserve for adjuvant therapy and rehabilitation.

When removing brain tumors, the principles of topographic approach of the tumor focus should be followed, taking into account the functional significance of the area of the planned surgical intervention. Therefore, when planning operations for the removal of glial brain tumors to optimize surgical approach (surgical access, volume of surgical cytoreduction of tumor tissue, intraoperative use of technical means), it is necessary to consider the results of preoperative neuroimaging and the clinical picture of the disease.

Modern neuroimaging methods used in clinical neuro-oncology offer the opportunity not only to detect signs of glial tumor growth in the early stages of the tumor process, but also to optimize a set of measures ensuring the effectiveness of surgical treatment. According to the results of multispiral computed tomography (MSCT), magnetic resonance imaging (MRI) (data from perfusion, diffusion, tractography, spectroscopy, functional MRI and angiography series), single-photon emission computed tomography (SPECT), as well as positron emission tomography (PET-CT) can provide information on the intracerebral tumor process. The multimodal combination of neuroimaging data allows one to get an idea of the histostructure of the tumor, the features of intrahemispheric spread and topographic relationships with adjacent structures, to establish the sources of blood supply and the intensity of tumor vascularization, its densitometric indicators, the nature of perifocal reactions, the degree of compression and translocation of brain structures, to verify signs of hypertensive - hydrocephalic syndrome and the level of occlusion of the cerebrospinal fluid pathway. In addition, the presence or absence of a cystic component, areas of necrosis, signs of concomitant hemorrhage can be detected in the neoplasm parenchyma. The information obtained is subject to critical analysis for planning surgical intervention, rational intraoperative use of technical means of surgical intervention, monitoring and comparison of preoperative and postoperative data.

The main standard requirements for performing neuro-oncological surgeries include protocol-recommended conditions for the use of modern surgical technologies, the use of sparing limited surgical approaches, a high degree of accuracy of approach to the tumor focus, compliance with the principle of precision of instrumental manipulations and technological processes of cytoreduction, ensuring the minimization of surgical trauma and the maximum preservation of adjacent anatomical stuctures (arterial vessels, venous collectors and subcortical tracts). In addition, the removal of brain tumors requires adequate anesthetic management and performing operation in real conditions of "bloodless" surgery. Thus, during surgery of glial tumors, it is possible to prevent appearance of the new neurological deficit or deterioration of the existing one, which is a prerequisite for improving the postoperative quality of life of patients.

Equipping the neurosurgical operating room with modern Hi-Tech equipment plays an important role in the implementation of these principles [3–5].

The introduction of advanced surgical technologies into clinical neuro-oncology has fundamentally changed the idea of surgical approach of the tumor, as well as the possibility of performing highly radical surgery in gliomas affecting functionally significant and vital brain structures, as well as in tumors with medial spread. Due to the technical perfection of means for performing neurosurgical operations in glial brain tumors, the survival rates and quality of life of patients have significantly improved.

The standard of surgery for brain tumors is the use of magnifying optics and microsurgical instruments. Modern operating microscopes (HAAG-STREIT, Zeiss, Leisa, Olimpus) offer the opportunity to carry out intraoperative angiography and fluorescence diagnosis of intracerebral infiltrative malignant tumors, to reproduce images obtained using neuroimaging methods of examination before surgery by layering in microscope glasses. Modern models of microscopes are equipped with surgical laser modules and endoscopic probes.

Surgical neuronavigation systems (Medtronic, BrainLab, Stryker, Radionics) are one of the leading technical means of modern neurosurgery, providing a qualitatively new level of neuro-oncological operations and contribute to increasing the efficiency of brain tumors surgery. The method of multimodal navigation with integration of MSCT, MRI, MR- angiography, MR-tractography, MR-perfusion and SPECT data is used for neuronavigation support of the surgery [6–9].

In the clinic of intracerebral tumors of the Institute of Neurosurgery named after Academician A.P. Romodanov, Ukraine using the "StealthStation TREON Plus" surgical neuronavigation system (Medtronic, USA), it was performed more than 2500 operations to remove brain tumors, mainly neuroectodermal tumors of the glial structure [10, 11].

The use of multimodal neuronavigation system in brain glioma surgery makes it possible to carry out virtual 3D modeling of topographic relationships between the tumor and adjacent anatomical structures, preoperative virtual planning of the surgery, to optimize the surgical approach and surgical trajectory ***(Fig.1)***. Such virtual preoperative and intraoperative orientation in three-dimensional space, created according to integrated multimodal data of neuroimaging studies, provides an opportunity to perforn controlled tumor resection with real-time intraoperative navigation support with video recording of the correlation of virtual three-dimensional images and the real operating field. Navigation support of the surgery creates conditions for controlled tumor resection within the limits determined by preoperative virtual planning, with simultaneous verification of the degree of the surgical intervention radicality [12–16].

Intraoperative neurophysiological monitoring is used to identify the functional limits of resection during neurosurgical manipulations when removing brain tumors localized within "critical" areas. This technique enables to carry out continuous monitoring of the functional state of the nervous system and timely detection of changes in performance indicators by recording sensorimotor evoked potentials or by stimulating the speech, motor or sensory cortex of the cerebral hemispheres. The technique of neurophysiological monitoring is the gold standard, the data of which correlate with the results of preoperative functional MRI and MRI tractography in the areas of localization of motor and language functions. The neurophysiological monitoring technique is most effective in preventing postoperative neurological deficits when combined with multimodal neuronavigation [17,18].

A qualitatively new level of surgical treatment of brain tumors is ensured by the introduction of the latest laser technologies in clinical neuro-oncology. Our experience in using laser methods includes 685 surgeries to remove intracerebral and extracerebral brain tumors utilizing as a source of high-energy laser radiation, the "Sayany MT" carbon dioxide laser (infrared radiation with a wavelength of 10.6 microns), YAG neodymium laser "Raduga" (infrared radiation with a wavelength of 1.06 microns), YAG holmium laser COHERENT "Versa Pulse Select" (infrared radiation with a wavelength of 2.1 microns), as well as semiconductor surgical lasers of domestic production ("Fotonika Plus", Ukraine) "Lika -surgeon" (wave generator of 0.808 microns with an output power of up to 30 W) and "Lika-surgeon M" (radiation with a wavelength of 1.47 microns, output power of up to 15 W). The latter belong to a new high-tech generation of compact laser surgical devices for brain tumor operations. Semiconductor laser devices are equipped with a laser pilot and a fiber light guide with an optical collimator at the distal end, provide stepwise regulation of laser radiation power, control of radiation parameters and exposure time.

Methods of laser vaporization and tumor ablation, laser thermal destruction of tumor invasion sites into functionally significant brain areas and tumor infiltration of the surrounding brain matter (perifocal zone), used in the removal of brain gliomas, simultaneously provide the effect of intraoperative laser hemostasis during laser exposure [19–22].

This article contains some figures that are displayed in color online but in black and white in the print edition.

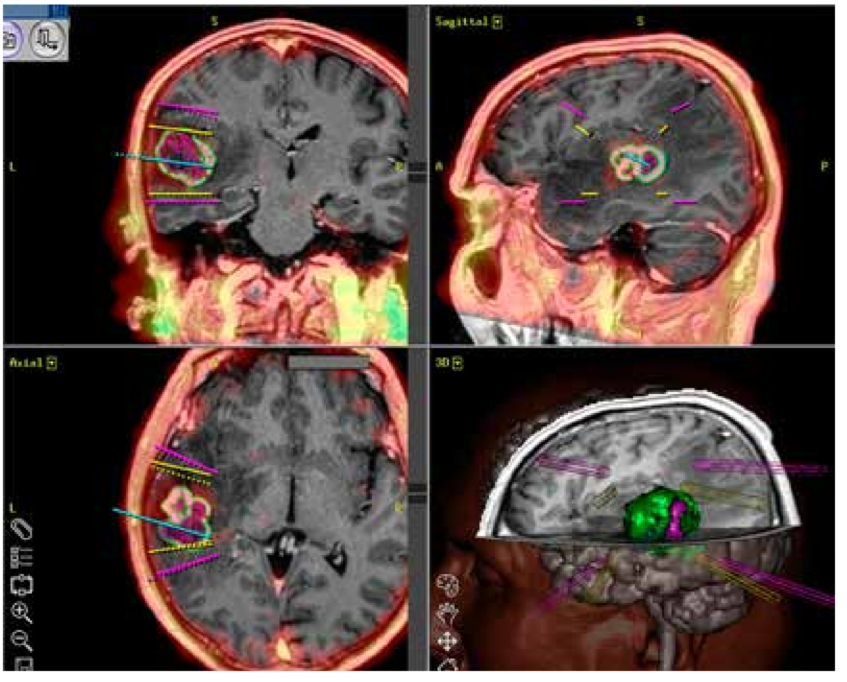

Fig. 1. Navigation 3D planning of surgical approach to a glial tumor

The advantages of using laser technologies in the removal of brain tumors include a high degree of precision of "laser" manipulations and strict localization of the targeted effect of the laser beam on biological tissue regardless of the depth of surgical approach, the non-contact nature of the laser tumor destruction process and the absence of mechanical impact on adjacent brain tissues, which significantly reduces the risk of surgery and prevents postoperative neurological deficits.

The impact of defocused laser radiation on the tumor tissue leads to its coagulation and devascularization, which ensures meticulous hemostasis and prevents delayed bleeding in the postoperative period. Tumor eradication involves laser irradiation and laser coagulation of the perifocal vascular network, which prevents early progression of the tumor process. In addition, the laser beam does not overlap the operating field and does not interfere continuous intraoperative telemonitoring and video recording during tumor resection, so the tumor is removed under constant visual control.

Based on the results of morphological studies of tumor tissue exposed to high-energy laser radiation, it was found that irreversible structural changes occur in the focus of laser thermal destruction, that is, the effect of tumor cytoreduction is achieved [23,24].

Given the irreversible nature of destructive changes occurring in tumor tissue under the influence of high-energy laser radiation, which leads to the death of tumor cells, intraoperative application of laser thermal destruction method eliminates the need for surgical cytoreduction of irradiated tumor tissue fragments in functionally important areas. This reduces the invasiveness of the operation and ensures anatomical and functional safety of brain structures. Laser thermal destruction of tumor tissue results in the effect of "death" of tumor cells is achieved, which is an analogue of radiosurgery, but of a fundamentally new level and high efficiency in terms of "destructive" characteristics [25,26].

The destructive effect (laser cytoreduction) caused by the impact of high-energy laser radiation on the tumor tissue was confirmed by the results of postoperative MRI and MSCT. According to neuroimaging data, a positive remote photodestructive effect of laser exposure on the structural elements of the tumor was established [27–31].

Laser thermal destruction of tumor tissue with intraoperative navigation support is an innovative technology in laser methods of brain tumor removal. Using the technology of navigated laser thermal destruction of brain tumors, 205 surgeries were performed to remove functionally significant and vitally important cerebral hemisphere tumors. Semiconductor surgical laser devices "Lika-Surgeon" and "Lika-Surgeon M" and the navigation system "StealthStation TREON Plus" (Medtronic, USA) were used [32–34].

Preoperative planning of laser removal of brain tumors is carried out using multimodal neuronavigation with three-dimensional reconstruction of cerebral hemispheres and tumor. The construction of a 3D model with the determination of anatomical and topographic relationships of the tumor with adjacent structures ensures the choice of optimal approach to the tumor, taking into account the topography of the gyri and sulci of the brain, venous collectors, main arteries and the trajectory of the direction of high-energy laser radiation for precise targeting of the tumor with control of surgical procedures and laser thermal destruction process.

For the neuronavigation support of "laser" surgery, the data of MSCT, MRI, series of fMRI, perfusion, diffusion and spectroscopy were used, which were combined in the form of a combined 3D image to identify hypervascularized heterogeneous tumor areas that are subject to laser-destructive exposure, or to determine areas of functional brain activity, which should be preserved.

Preoperative 3D planning also included segmentation and three-dimensional contouring of the tumor, the area of perifocal edema, and surgical approach boundaries. Technological features of the multimodal neuronavigation software allow to display combined images of neuroimaging data in combination with virtual 3D surgery planning data on the screen of the navigation station telemonitor. During laser surgery, the results of virtual 3D planning of the operation using the intraoperative video monitoring system were compared in real time with images of the operating field, in particular with the area of tumor laser thermal destruction.

The planned volume of laser thermal destruction of the glial tumor was finally corrected intraoperatively, comparing the data of virtual multimodal spatial images and objective information from the laser exposure zone, continuously obtained in real time ***(Fig. 2, 3)***.

To increase the degree of radical tumor resection invading functionally important areas and median structures, laser irradiation under the control of neuronavigation was applied to tumor areas that spread to areas of high surgical risk.

Intraoperative use of fMRI results in the multimodal navigation system allows identifying and "visualizing" activity zones in the sensorimotor cortex of the cerebral hemispheres, determining their relationship with the tumor, and reducing the degree of possible traumatization of functionally important areas during laser thermal destruction. The results of magnetic resonance venography must be taken into account. Computer reconstruction of convexitally located venous collectors allows optimizing the area and boundaries of safe transcortical surgical approach, determining the spatial trajectory of the approach to the tumor, which provides adequate conditions for laser-surgical manipulations within the operating field. In addition, venous collectors are used as topographic landmarks for navigation support during the laser stage of the surgery.

The computer combination of SPECT and MRI/MSCT data in a single image is of great importance in multimodal navigation planning of the operation to increase the information content of each method. SPECT makes it possible to "visualize" tumor areas with the highest proliferative activity, and when combined with MSCT and MRI images, determines the topography of tumor focus, in particular its components, vascularization features, perifocal reactions. Combined MSCT/SPECT and MRI/SPECT images enable to visualize the necrotic and cystic components of glioma, to contour "living" tumor tissue, to differentiate tumor tissue and perifocal edema zones, and to obtain an idea of the histobiological characteristics of the tumor. The use of multimodal navigation with a combination of MRI/SPECT or MSCT/SPECT images allows a controlled targeted laser-thermal treatment on the tumor tissue. The defocused laser beam provides an opportunity under navigation control to coagulate and devascularize the tumor tissue, followed by its laser thermal destruction and vaporization. The use of laser thermal destruction of active tumor growth zones increases the radicality of surgery and reduces the risk of injury to adjacent brain structures.

Accuracy of laser thermodestructive treatment direction during surgery is controlled by comparison of virtual MRI/SPECT and MSCT/SPECT images with real time continuous telemonitoring data, which allows dosed exposure to residual tumor tissue areas that spread into functionally important areas and median structures, in the conditions of intraoperative visualization of the boundaries of the irradiation zone [9].

When the tumor is located in the precentral and postcentral areas with the spread of the process in the zone of motion activity, the results of MR tractography are important for targeted laser thermodestruction. The introduction of MR tractography data into the navigation system makes it possible to establish the degree of dislocation and destruction of fibers of conducting

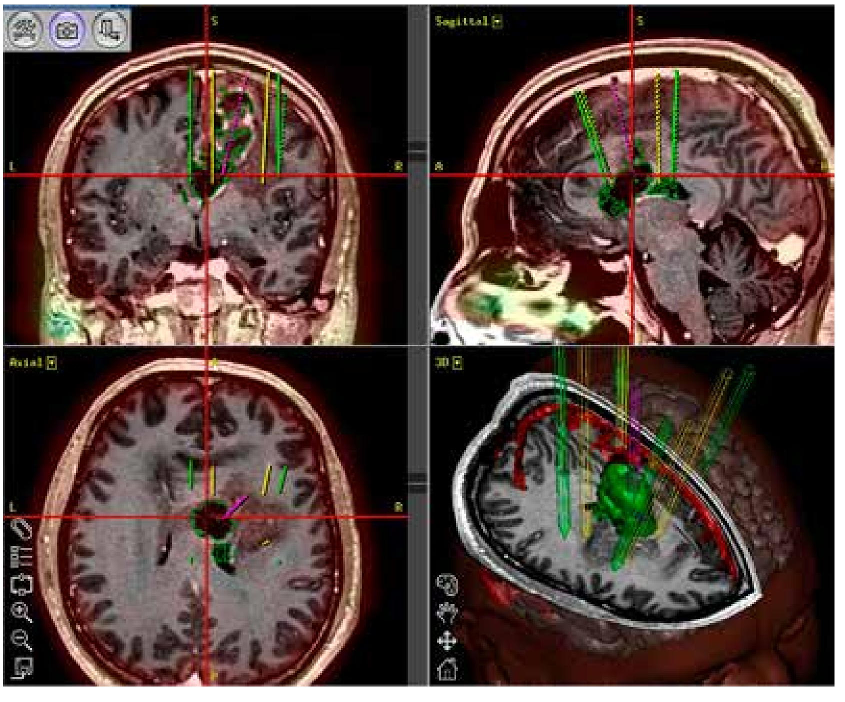

Fig. 2. Virtual navigation 3D-planning of surgical approach for laser resection of a tumor in a medially located tumor

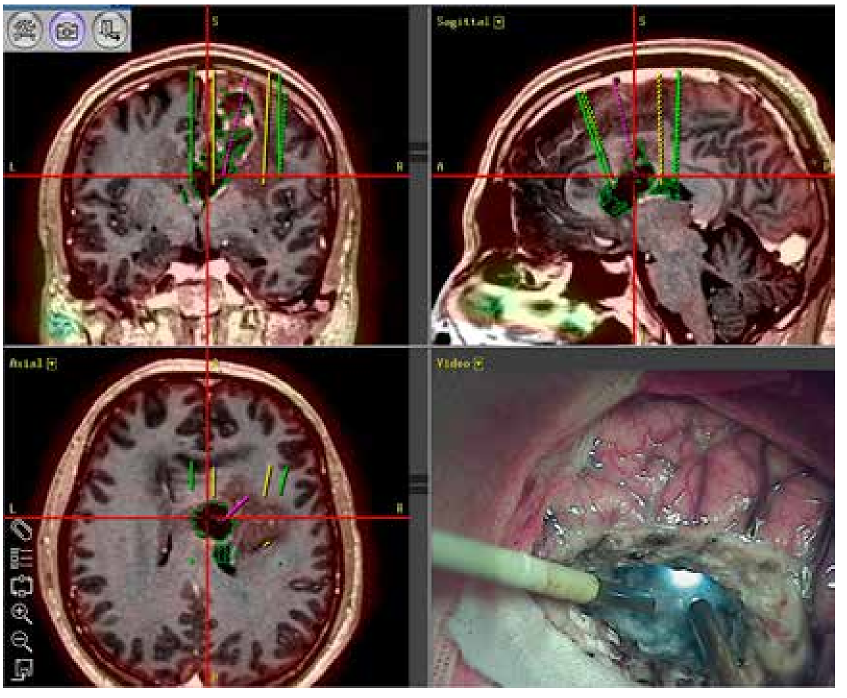

Fig. 3. Laser destruction of a medially located glial tumor with intraoperative navigation support

pathways. Determining the spatial relationships of the tumor with adjacent areas of the motor cortex and subcortical conducting pathways enables to perform laser thermal destruction of the tumor tissue directly along the fibers, the topographic projection of which is controlled using the method of spatial reconstruction of a three-dimensional virtual model. Due to the use of innovative navigation and laser technologies during the resection of brain gliomas, the proportion of patients with Karnofsky index ≥70 points has increased from 57.3 to 86.4%.

The possibilities of laser-surgical methods of removing glial tumors of the brain are expanding with the use of neuroendoscopic technologies. Endoscopic technique in intracranial laser surgeries is used both as a fundamental tool for minimally invasive surgery, and as an auxiliary assisting surgical tool. During transendoscopic laser surgeries, high-energy laser radiation is transported using a fiber light guide inserted into one of the endoscopic channels [35,36].

Based on our own clinical experience in the use of laser and navigation technologies in neuro-oncological practice, a fundamentally new method of laser surgeries for malignant tumors of intraventricular localization and median brain tumors using transendoscopic navigated laser thermal destruction and interstitial thermotherapy was developed.

Laser irradiation of the tumor was performed with the help of fiber light guide using a neuroendoscope (Tian Song, China) equipped with a digital endoscopy system with HD image quality UC-100 (North-Southern Electronics, China).

Using multimodal navigation technology, preoperative planning of surgical intervention was performed with the construction of virtual 3D model of brain and tumor, optimal surgical endoscopic approach to the tumor was formed outside the functionally important areas and conducting pathways of the brain, there were specified the orientation of the focus of laser destruction and the trajectory of high-energy laser radiation guidance to tumor tissue, and there were determined functionally allowed limits of laser thermal destruction. The laser-endoscopic stage of the operation was performed under constant navigation control ***(Fig. 4, 5)***.

The use of endoscopic assistance enables to visualize the process of laser irradiation of tumor areas infiltrating the functionally important areas of the brain in real time. Real-time telemonitoring was performed during the surgical intervention.

Surgeries with laser-endoscopic technologies, preoperative navigation virtual 3D planning and intraoperative navigation support of the laser thermodestruction process is a fundamentally new highly effective method of laser cytoreduction of brain tumors, which allows performing surgeries of increased radicality when the tumor spreads to the vital median structures of the cerebral hemispheres. Performing neuroendoscopic laser surgery accompanied by navigation provides targeted delivery of laser radiation to the area of tumor involvement in "critical" brain areas with minimal surgical approach, enables visual control of the process of laser thermal destruction while preserving the anatomical and functional integrity of adjacent brain structures [37–41].

Mobile magnetic resonance (for example, PoleStar, USA) and computer (for example, CereTom, USA) tomographs can be used for intraoperative verification of the radicality of the surgical intervention and determination of the distant tumor volume, if necessary.

The innovative technology which is used in the intraoperative magnetic resonance imaging allows it to be used together with surgical navigation. The results of intraoperative MR imaging can be automatically integrated into the navigation station system, allowing the planned navigation support of the tumor removal process to be adjusted [42,43].

A promising method of laser thermal destruction of malignant brain tumors is the use of multimodal navigation in the conditions of intraoperative fluorescence imaging of malignant tumors using 5-aminolevulinic acid, which enables to identify the boundaries of intracerebral tumor and perform tumor tissue irradiation without damaging the adjacent brain matter. In neuro-oncology, the drug Gliolan (5-aminolevulinic acid hydrochloride) is used to remove intracerebral tumors [44–50].

The technology of combined navigation laser thermal destruction and photodynamic therapy (PDT) can be considered as a highly effective method of increasing the radicality of surgical interventions for infiltratively growing intracerebral tumors.

In malignant glial tumors, drugs synthesized on the basis of the active substance chlorin E6 (chlorin E6) are used for PDT, which selectively accumulates in malignant tumors and when exposed to radiation with a wavelength of 660–670 microns causes the destruction of tumor cells and cytoreduction of tumor tissue. The results of our earlier experimental studies on the problem of PDT of glial tumors and literature data on the clinical application of this method indicate the prospects and feasibility of the widespread use of the PDT method in neuro-oncology [51–57].

An innovative method of ensuring the radicality of surgical intervention in brain gliomas is the intraoperative use of the X-ray therapy system Intrabeam® ZEISS Medical Technology (Germany). The

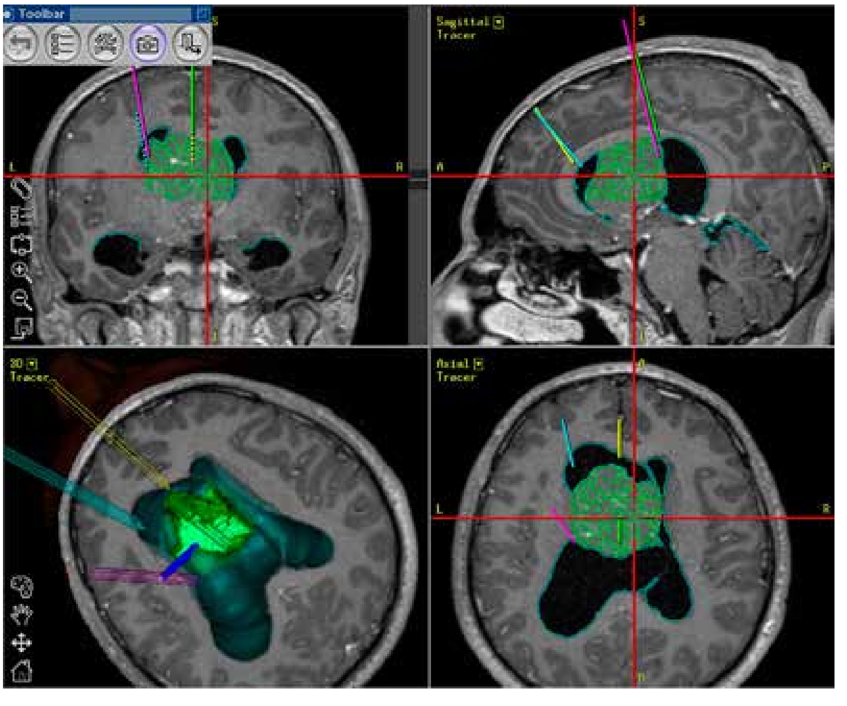

Fig. 4. Navigation 3D planning of transendoscopic resection of intraventricular tumor

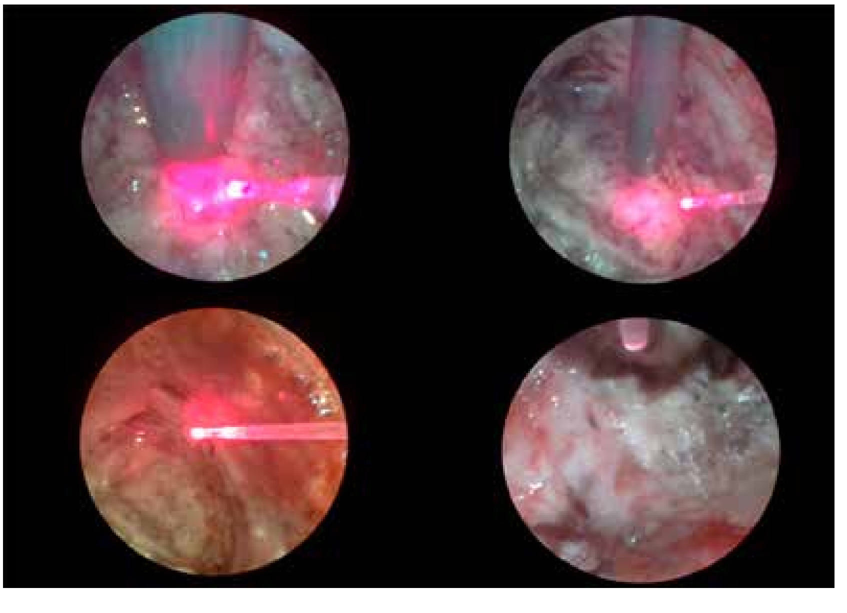

Fig. 5. Transendoscopic laser resection of intraventricular tumor under neuronavigation control

tumor tissue is irradiated in the open operating field with the help of an applicator introduced into the bed of the distant tumor, in the center of which the source of X-rays is located. The Intrabeam® system provides a targeted high-dose radiation exposure to the perifocal zone of tumor infiltration without damaging adjacent brain structures [58,59].

With the introduction of advanced surgical technologies into neuro-oncology, the concept of the surgical approach of the tumor, the possibility of performing more radical surgeries for tumors of functionally significant and vital brain structures has changed, the level of intraoperative risk of traumatizing brain structures surrounding the tumor, the main arteries and large venous collectors has decreased.

Modern innovative technologies of surgical treatment of malignant glial tumors not only increase the radicality of surgical intervention, but also provide in some cases the possibility to remove the tumor with a high postoperative level of the patients' quality of life.

Postoperative treatment of patients with brain gliomas (radiation therapy, chemotherapy and immunotherapy) is performed taking into account the results of histological examination, immunohistochemical determination and molecular diagnosis in accordance with the new "Classification of tumors of the central nervous system 2021" [60].

Conclusions

The use of highly informative neuroimaging methods and innovative advanced laser, navigation and endoscopic technologies in clinical neuro-oncology ensures high efficiency of surgical treatment of patients with brain tumors of the most complex topographic and anatomical localizations, which meets the tasks and requirements of modern neuro-oncology. Individualization of treatment measures for brain tumors using modern methods of diagnostic neuroimaging and intraoperative application of innovative navigation, laser and endoscopic technologies is necessary.

The use of advanced technologies of brain tumor resection allows preserving the anatomical and functional integrity of adjacent brain structures, main arteries and venous collectors, which, provided the surgical intervention is radical, ensures a high postoperative quality of life for patients

Considering promising directions in the surgical treatment of patients with brain tumors, it should be taken into account that neuro-oncology develops in conjunction with scientific and technical progress.

The success of surgical neuro-oncology depends on the level of scientific research of current trends in neurosurgery, the degree of introduction of innovative technologies, the volume of investments involved in the medical industry, the stability of the national economy with the funding of medicine at the level of about 8% of the gross domestic product.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This article is a literature review, therefore no ethics committee approval was required.

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