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METABOLIC NAVIGATION DURING BRAIN TUMOR SURGERY: ANALYSIS OF A SERIES OF 403 PATIENTS

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Introduction. Metabolic navigation with 5-ALA is one of methods for intraoperative imaging in neuro-oncology.
Aim. To perform a comparative analysis of sensitivity of metabolic navigation with 5-ALA during surgery of primary and secondary brain tumors of various histological nature and degree of malignancy.
Materials and methods. During the period from 2013 to 2020, our group have performed surgery to 403 patients using metabolic navigation: microsurgical resections were performed in 384 people with brain tumors, 220 of them were with glial tumors, 101 were with intracranial meningiomas, 63 were with metastatic brain damage. Among patients with metastases, 39 patients had a solitary injury, 16 had a multi-focal injury, so 72 cases of metastatic nodes were considered in this group. Stereotactic biopsies with 5-ALA-assistance were performed in 19 people. Metabolic navigation was performed with the drug 5-ALA, which was taken orally at a dose of 20 mg/kg 2 hours before surgery. Intraoperative fluorescence was evaluated using microscope with a fluorescent module.
Results. Metabolic navigation using microscope has a high sensitivity when employed during microsurgery (including repeated implementation of surgery) in cases of anaplastic gliomas (65 % in total, 58 % with bright glow), glioblastomas (94 % in total, 53 % with bright glow), intracranial meningiomas (94 % in total, 64 % – with bright glow). The use of 5-ALA has significant limitations in sensitivity in cases of diffuse gliomas (46 % – in total, 27 % – with bright glow) and brain metastases (in total 87 % – for the solid part, 52 % – for the bed, with bright glow – 51 %). In diffuse gliomas, the glow areas had significantly higher proliferative index and cell nuclei density than the fluoronegative zones. Among the most important factors affecting the glow of gliomas it can be noted: the status of the *IDH1* mutation, the volume of the contrasting part of the glioma according to MRI data, the methionine accumulation index according to positron emission tomography, the tumor blood flow indicators according to the arterial spin marking method – ASL perfusion.
Conclusions. Implementation of 5-ALA navigation with the use of microscope provides high sensitivity in cases of glioblastomas, anaplastic gliomas (especially for detecting of non-contrasting part of tumor that is not visually altered in the white light of operating microscope) and brain meningiomas. The method is less effective in low-grade gliomas and intracranial metastases.

Keywords: metabolic navigation, brain tumors, 5-ALA, protoporphyrin, fluorescence

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INTRODUCTION

The recommendations for neuro-oncological surgery include information on maximum tumor resection with minimal risk of functional complications with the mandatory use of preoperative planning (functional magnetic resonance imaging (fMRI), tractography), microsurgical techniques and intraoperative optics [1]. Reliable information about the volume of tumor to be resected can be obtained by intraoperative imaging. The problem solution is mainly achieved by employment of optical systems (operating microscopes and endoscopes), intraoperative computer tomography, MRI, ultrasound scanning and three-dimensional frameless ultrasound neuronavigation, neuronavigation systems, metabolic navigation (MN) and various combinations of these methods [1, 2].

Taking into account that the possibilities of using intraoperative MRI are limited, and intraoperative ultrasound examination does not provide information about the metabolic parameters of the tumor, then development and improvement of intraoperative optical neuroimaging and optical spectroscopy methods in neuro-oncology are relevant [3].

One of the main intraoperative imaging in surgery of brain tumors of various histological nature is the MN technique. In 1947, the first clinical report was published on the use of fluorescein during neurosurgical removal of brain tumors in 46 patients, which before the advent of neuroimaging methods contributed to more accurate determination of tumor localization during surgery [4]. At the end of the 20th century, the first data on the possibility of implication of 5-aminolevulinic acid (5-ALA) in neurosurgery, mainly of malignant gliomas (GL) [5], were reported.

Currently, the 5-ALA is used in surgery of other brain and spinal cord tumors in both children and adults, in particular in cases of meningiomas [6], metastases [7, 8], neurocytomas, ependymomas [9] and other neoplasms of brain and spinal cord.

The aim of the study is to generalize the experience of surgical treatment of brain tumors of various histological nature – low and high-grade GL, intracranial meningiomas (ICM) and metastases (ICMs), as well as to compare the sensitivity of fluorescence (FL) in tumor surgery

MATERIALS AND METHODS

Clinical characteristics of patients

The work is a single-center cohort study. For the period from 2013 to 2020 at the Burdenko Neurosurgical Institute 403 patients has undergone surgery using the MN: microsurgical resections were performed in 384 people with brain tumors, including 220 with glial tumors, 101 with ICM, 63 with metastatic brain lesion. Among patients with metastases, 39 patients had a solitary lesion, 16 had a multi-focal lesion, so 72 cases of metastatic nodes were considered in this group. Stereotactic biopsies (STB) with the 5-ALA assistance were performed in 19 people. A detailed distribution of cases with consideration of histology outcome is presented in Table 1. The study included 183 men and 220 women, the mean age of patients was 46 ± 15.3 years, the minimum age was 17, the maximum was 78 years.

The technique of microsurgical operative interventions using fluorescence in brain tumors

After informed consent and providing data on the absence of significant pathology of liver and kidneys, patients received a solution of 5-ALA hydrochloride (Alacens®, SSC "Research Institute of Organic Intermediates and Dyes", Russia) at a dose of 20 mg/kg. The 5-ALA was prescribed 2 hours before surgery (90 % of patients) or 3–4 hours before (9 % of patients), less often the drug was administered immediately before the patient was taken to the operating room (1 % of observations). The surgeries were performed using the Pentero microscope with FL module (Carl Zeiss) – in BLUE 400 mode. At the time of surgery, the operating room was darkened (external light was turned off), the neurosurgeon performed periodic switching of the white light and FL mode. The work near functionally significant zones was carried out in accordance with data of neurophysiological monitoring. In case of severe bleeding at the main stage of tumor removal, a staged hemostasis was first performed followed by switching the microscope to the FL mode.

The intensity of FL was assessed subjectively in the eyepieces of the microscope: bright (intense red staining), moderate (pink), weak (pale pink), no glow. An objective assessment of the luminescence was performed in 46 observations using the laser spectroscopy method.

In the case of STB, the glow of the biopsy specimen was evaluated immediately after its extraction from Nashold cannula on Petri dish under the fluorescent light of a microscope.

RESULTS

1. Comparative analysis of fluorescence diagnostics sensitivity in surgery of gliomas, intracranial meningiomas and metastases

The most effective use of fluorescence diagnostics (FLD) was in the surgery of ICM and GL of a high degree of malignancy (see Table 1).

Gliomas. Among high-grade GL, up to 12.9 % of tumors are fluoronegative, while their frequency in the group of anaplastic GL (Grade III tumor malignancy) reaches 34.5 % and in the group of fluoronegative GL – up to 6 %. As a result of the study, a reliable influence of the tumor malignancy degree (Grade) on the fact of luminescence and its degree during surgery was established, the relationship was statistically significant ($p < 0.05$). The most frequent bright FL was observed in patients with anaplastic GL (58 %), which was probably due to absence of necrosis zone in them as compared to patients with glioblastomas (53 %). It is interesting to note that 10 % of glioblastomas had a weak degree of tumor luminescence as compared with 32 % in patients with low-grade GL (see Table 1).

The analysis has shown that the FL-effect in the group of patients with cerebral GL was significantly influenced by the following factors: administration of anticonvulsants before surgery; volume of contrasted part of the GL; level of volumetric blood flow in tumor according to perfusion studies; methionine accumulation index according to preoperative positron emission tomography (PET); GL subtype and presence of mutation. The fluorescent effect did not significantly depend on the fact of repeated surgery.

Among Grade II–III GL, the density of cell nuclei was significantly higher in the tumor glow zone than in the non-luminous one (2180 ± 920 *vs* 1510 ± 630 mm^2, $r = 0{,}68$, $p = 0.03$). The proliferative index Ki-67 was also significantly higher in the tumor glow zones of 7.41 ± 2.2 *vs* 2.52 ± 1.1 % ($r = 0.62$, $p = 0.04$). The use of MN made it possible in 7 (25.9 %) out of 27 cases to identify an anaplastic focus and diagnose GL of Grade III when performing multiple biopsies and taking biopsies from the fluorescent and non-fluorescent parts of the tumor with targeted biopsy from the glow zone. At the same time, the main part of the tumor did not fluoresce (GL of Grade II).

Table 1. *Comparative analysis of metabolic navigation sensitivity during microsurgical removal of brain gliomas of low (LGG) and high (HGG) malignancy, intracranial meningiomas (ICM) and metastases (ICMs)*

Histological tumor type, malignancy degree	Number of cases		
	total, *n*	with fuorescence, *n* (%)	without fuorescence, *n* (%)
LGG	**56**	**26 (46.4)**	**30 (53.6)**
Piloid astrocytoma, Grade I	3	3 (100)	0 (0)
Diffuse astrocytoma, Grade II	24	6 (25)	18 (75)
Hemistocytic astrocytoma, Grade II	3	3 (100)	0 (0)
Ganglioastrocytoma, Grade II	1	0 (0)	1 (100)
Infantile desmoplastic ganglioglioma	1	1 (100)	0 (0)
Oligoastrocytoma, Grade II*	16	8 (50)	8 (50)
Oligodendroglioma, Grade II	6	3 (50)	3 (50)
Pleomorphic xanthoastrocytoma, Grade II	2	2 (100)	0 (0)
HGG	**164**	**143 (87.1)**	**21 (12.9)**
Anaplastic astrocytoma, Grade III	29	19 (65.5)	10 (34.5)
Anaplastic oligoastrocytoma*, Grade III	8	5 (62.5)	3 (37.5)
Anaplastic oligodendroglioma, Grade III	6	4 (66.7)	2 (33.3)
Glioblastoma, Grade IV	115	108 (94)	7 (6)
Gliosarcoma, Grade IV	6	6 (100)	0 (0)
ICM	**101**	**95 (94.05)**	**6 (5.95)**
Grade I	78	75 (96.2)	3 (3.8)
Grade II	21	18 (85.7)	3 (14.3)
Grade III	2	2 (100)	0 (0)
ICMs, a solid part	**63****	**55 (87.3)**	**8 (12.7)**
Lung cancer	24	21 (87.5)	3 (12.5)
Breast cancer	19	17 (89.4)	2 (10.6)
Other metastases	20	17 (85)	3 (15)
Total	*384*	*302 (78.7)*	*82 (21.3)*

**Retrospective analysis of histological material (2012–2020): some patients that have undergone surgery before 2016 had mixed gliomas – oligoastrocytomas and anaplastic oligoastrocytomas.*
***72 tumor foci were recorded in patients with ICMs (n = 63); the table shows data from patients as a whole.*

Intracranial meningiomas. Of 101 (100 %) patients with ICM, 95 (94.05 %) patients had intraoperative tumor FL. When assessing visible FL through an operating microscope, bright FL was observed in 60 (63.15 %), moderate – in 23 (24.2 %), weak – in 12 (12.63 %) patients. The median age of patients with fluoropositive tumors was 56 years (from 25 to 79 years, $n = 95$), of those with non-fluorescent meningiomas – 41.5 year (from 38 to 59 years, $n = 6$), the differences between the age groups were statistically significant ($p = 0.02$).

The following factors did not significantly influence ($p > 0.05$) the FL-effect during surgery: the degree of malignancy of meningioma and its localization, administration of decongestant and anticonvulsant drugs, histological subtype of meningioma, presence of concomitant diseases, the fact of repeated surgery. The fact of intraoperative bleeding significantly influenced ($p < 0.05$) the tumor glow during resection. The blood in the wound blocks the FL-effect due to its high optical density.

After removal of the main tumor node, the FL-glow was recorded: in 10 cases – the dura mater (DM) lesion that was not visible in white light, in 5-arachnoid membrane lesion of adjacent vessels, in 4 – adventitia of vessels underlying the tumor, in 11 – hyperostosis of lesioned bone, in 6 – small residual fragments of the tumor that were not visible in white light. Thus, in 36 (35.6 %) of 101 patients additional areas of meninges lesion related to residual fragments of the tumor were revealed during the removal of ICM – in dura and arachnoid mater; while in 27 (26.7 %) observations, surgical technique was adjusted: additional resection of the lesioned DM, grinding of fluorescent areas of hyperostosis with boron or removal of the bone flap, residual fragments of the tumor, coagulation of the underlying arachnoid matter lesioned by the tumor.

Intracranial metastases. In present study, the MN was used in 63 patients with ICMs. Visible FL was registered in 61 (84.7 %) of 72 tumor foci, of them weak FL – in 14 (22.9 %), moderate – in 16 (26.3 %), pronounced – in 31 (50.8 %) foci. Absence of the FL was recorded in 11 (15.3 %) foci.

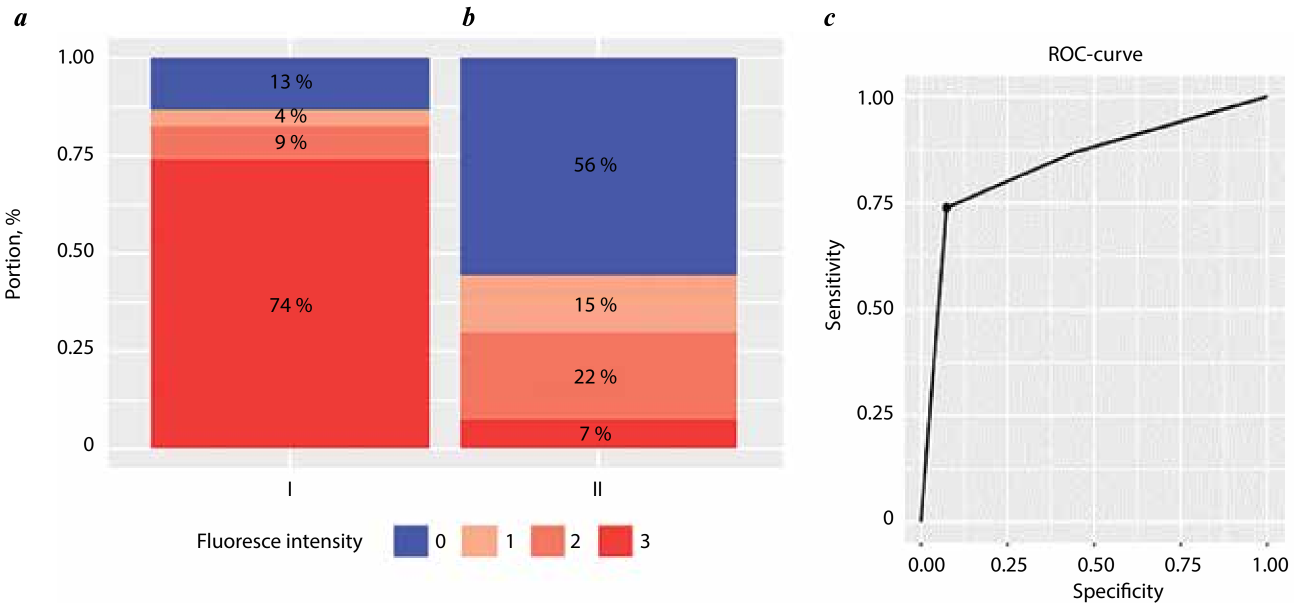

Fig. 1. *The relationship between fluorescence in the bed of removed malignant glioma and the presence (a) or absence (b) of tumor cells in it; I – there are tumor cells in the bed; II – there are no tumor cells in the bed; ROC curve (c): with a bright glow, the sensitivity of detecting tumor cells in the bed is 74 %, specificity – 92.5 %*

Bright FL was significantly more common in lung cancer metastases (81 %) as compared with breast cancer (22.2 %). In adenocarcinoma cases, the bright glow was significantly less frequent ($p < 0.05$).

The degree of brain metastases luminescence is significantly influenced by the primary source. Thus, the intensity of FL was significantly higher in lung cancer group (the frequency of bright glow – up to 81 %), while the lowest intensity of FL was observed in breast cancer group (the frequency of weak glow – up to 50 %). In addition, such factors as intraoperative bleeding ($p < 0.05$) and time elapsed after radiosurgical exposure (preoperative radiosurgery) ($p < 0.05$) significantly influenced the FL-effect.

2. Metabolic navigation during stereotactic biopsies of intracerebral tumors

This subgroup included 19 patients – 11 men and 8 women, aged from 29 to 77 (median – 50) years. Frame stereotaxis supplied with the CRW system (Integra Radionics, USA) was used in 16 cases, in 3 cases – it was the ROSA robotic system. The glow of tumor biopsies in STB with the 5-ALA was obtained in 12 (63.1 %) of 19 patients. Fluorescence was more typical for patients with lymphomas and GL of high degree of malignancy: in 10 (83.3 %) of 12 patients, while in 50 % of the cases there was a bright glow. The analysis of fluorescent biopsies in patients with high-grade GL and lymphomas (20 biopsies from 10 patients) revealed tumor cells in all of the samples.

3. Analysis of fluorescent bed glow in patients with gliomas of high malignancy and intracranial metastases

The study of postoperative cavity in the bed of removed GL of high malignancy was performed in 75 patients (21 anaplastic astrocytomas, 8 anaplastic oligodendrogliomas, 46 glioblastomas). In 50 patients, visual assessment of the removed tumor bed in white light revealed no tumor remnants. However, in 32 (64 %) of 50 patients, the glow of tumor perifocal zone in the bed was revealed. At the same time, a bright glow was observed in 18 (36 %), moderate – in 9 (18 %), weak – in 5 (10 %) patients. When there was bright glow in the bed of removed GL of high degree malignancy, the detection rate of tumor cells in biopsies was 74 %, the specificity was 92.5 % (Fig. 1).

Of 63 patients having had metastases surgery in 56 (89 %) observations the bed of the removed formations was fluorescent, of them from 22 patients the multiple biopsies from the bed was taken to assess the presence or absence of tumor cells in it. The 48 biopsies were examined in total: in 25 (52 %) of them tumor cells were detected in the FL zone, in 23 (48 %) no tumor cells were detected in fluorescent biopsies.

4. Laser spectroscopy in surgery of intracranial meningiomas and metastases

Quantitative spectroscopy was performed in 46 patients with ICM and ICMs. The laser spectroscopy revealed accumulation of protoporphyrins (PP) in 46 observations with no visible glow in the microscope eyepieces in 11 (23.9 %) patients; it was also revealed in patients with ICMs that index of PP IX accumulation varied from 9.39 to 121.93 relative units, that in average was 39.92 (min – 9.39, max – 121.93) relative units. In the hyperostosis zone, the PP accumulation indices were significantly lower (as compared with the solid part of the tumor) – 14.6 (min – 7, max – 19.6) relative units ($p = 0.04$). A significant correlation was revealed between qualitative assessments of FL via microscope and indicators of quantitative PP IX accumulation

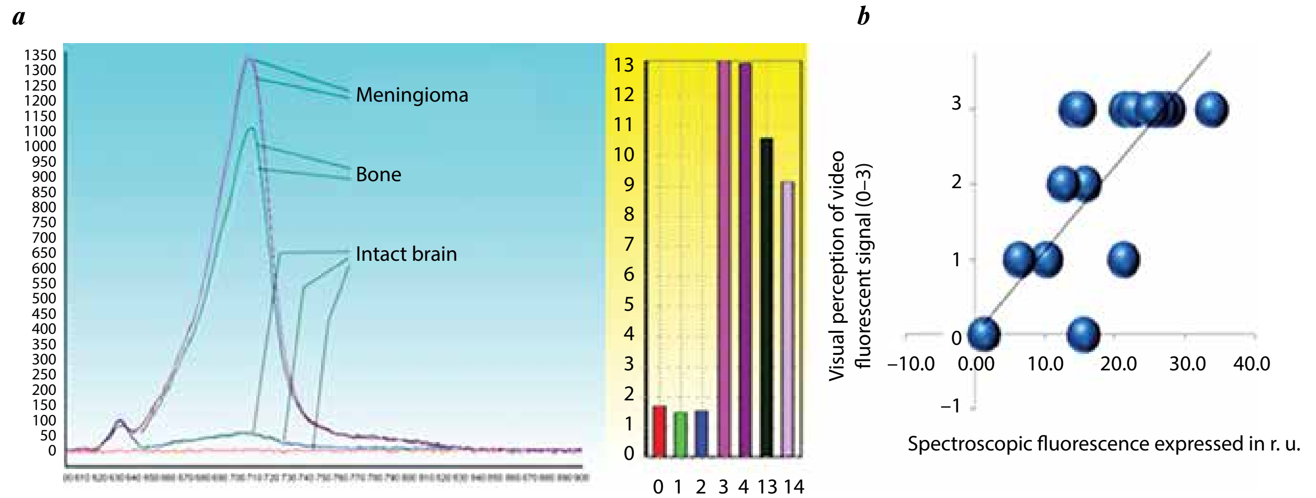

Fig. 2. *Spectroscopy parameters during removal of intracranial meningioma in the solid part of tumor and the hyperostosis zone (a), correlation between fluorescence from the microscope and spectroscopy (b)*

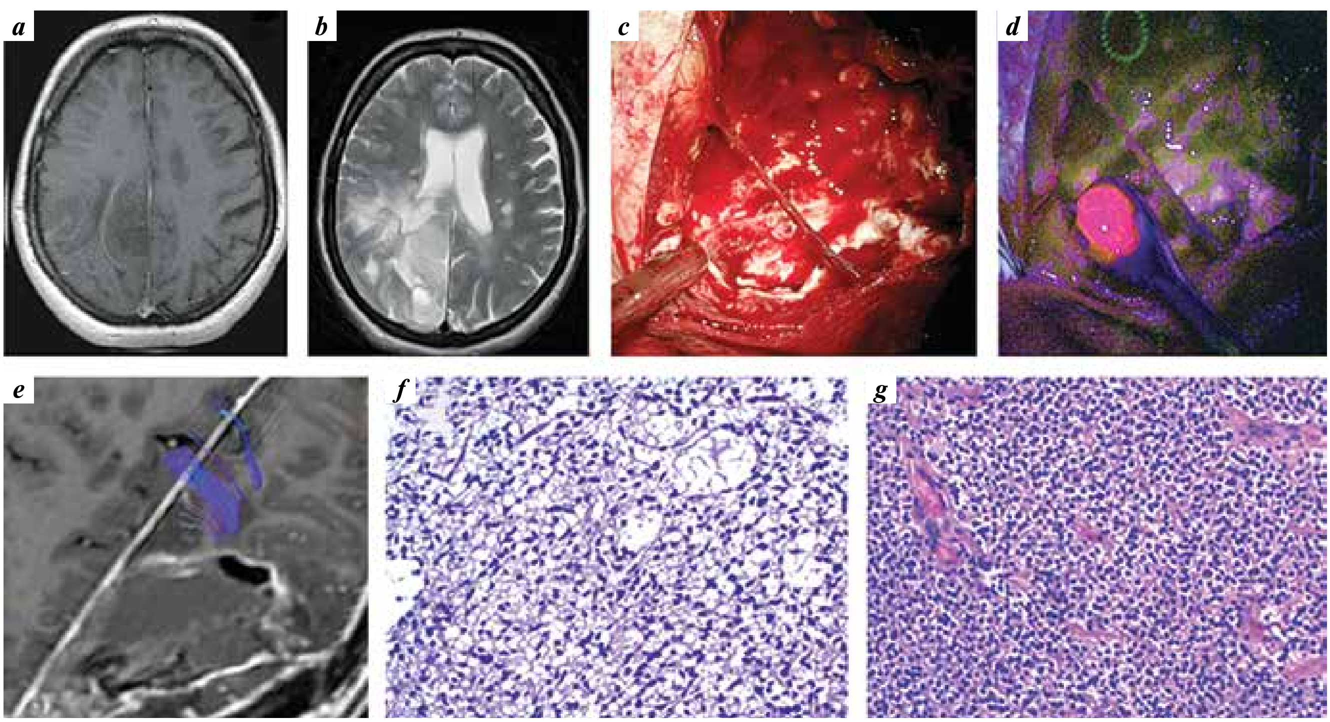

Fig. 3. *An example of focal glow of biopsy from patient with Grade III anaplastic astrocytoma; the biopsy was taken from the luminous part of glioma (Grade III site), the main part of the tumor did not fluoresce (Grade II site). Preoperative MRI (axial section): a – T1 with contrast, b – T2; intraoperative photographs: c – performed in white light, d – in FL modes (there is bright glow of one tumor area with absence of FL in the rest part of it); e – postoperative MRI (T1 with contrast enhancement); morphological examination of the biopsy: f – sample is from main non – fluorescent part of the tumor (Grade II site), g – sample on the right is from small fluorescent part of the tumor (Grade III site)*

(relative units) obtained using laser spectroscopy ($r = 0.82$; $p < 0.001$) (Fig. 2).

Measurement of the PP accumulation spectra in patients with ICMs has revealed that level of protoporphyrins was significantly lower (as compared with patients with meningiomas) – in case of bright glow the mean FL index was 35 (22–42), for moderate – 18.5 (15–22), for weak – 9 (8–11) relative units. In case of absence of the visible glow the mean FL index was 7.5 (6–9) relative units.

CLINICAL EXAMPLES

Clinical example 1

Patient Zh., *34 years old, intracerebral tumor of the right parietal lobe with germination into deep structures (corpus callosum, lateral ventricle, subcortical ganglia) (Fig. 3). The main part of tumor is of Grade II that did not display fluoresce during surgery. However, during resection a small focus of bright glow was revealed (Fig. 3 d); during histological examination of samples from this area it turned out that it corresponded to a Grade III tumor, anaplastic astrocytoma IDH1+.*

Clinical example 2

Patient Zh., *61 years old. Combined use of FLD and surgery with intraoperative "awakening" in patient with glioblastoma of the left frontal lobe (Fig. 4). During the surgery at the stage of tumor removal speech disorders in the form of combined aphasia were noted. Resection was stopped, the patient had residual FL in the bed. Combined aphasia was noted in the neurological status during postoperative period: motor aphasia in combination with amnesic and dynamic ones, produced by interruption of connections between the left frontal and temporal lobes due to partial damage to the arcuate bundle during surgery. A complete regression of aphasia phenomena was observed by the 7th day of postoperative period. Histological examination: glioblastoma IDH1 NOS.*

Clinical example 3

Patient S., *37 years old, with convexital meningioma (Grade I) of the right parietal region. There were general cerebral symptoms. Bone-plastic trepanation with removal of meningioma and lesioned DM was performed. When the FL-mode was turned on, bright FL of the DM sites along the matrix edges and FL sites on the adventitia of vessels in the bed of removed meningioma were recorded. Additional resection of DM with FL-sections was performed as well as the DM plastic surgery with a free periosteal flap. A biopsy of fluorescent adventitia of cortical vessels was not performed due to risk of disruption of local cortical blood flow. The wound healing took place by primary tension. The course of postoperative period was without peculiarities. The radicality of the surgery is grade II of D. Simpson classification (Fig. 5).*

Clinical example 4

In the ***patient Zh.,*** *who was 60 years old, multiple metastases of breast cancer in the brain were revealed. During the surgery, there was a weak FL of the removed tumor bed. The results of an additional biopsy from the glow zone: no tumor cells were detected. Conclusion: the FL in the bed is caused by PP IX synthesis in edematous brain tissue (Fig. 6).*

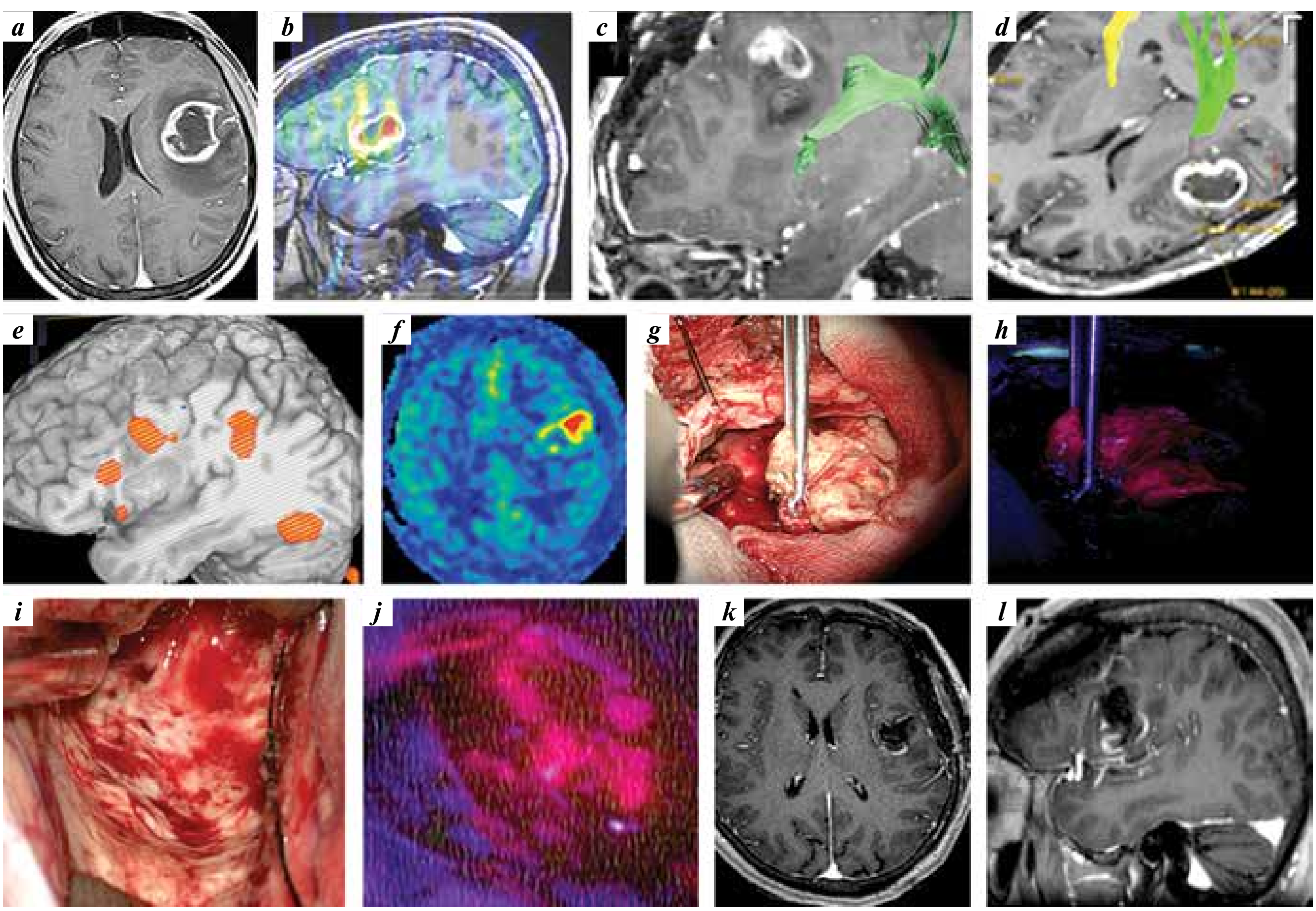

Fig. 4. *Combined use of metabolic navigation and craniotomy in awake patient with glioblastoma of the left frontal lobe in the Broca's area: a – MRI (T1 with contrast), axial section; b – MRI (T1, sagittal section), combined with ASL perfusion; c – MRI-tractography of arcuate bundle (near tumors, part of the fibers in frontal portion of the tract is not revealed – this is the zone of edema-infiltration); d – MRI-tractography with construction of a pyramidal tract, the tract is outside the tumor; e – preoperative functional MRI (the Broca's area is mapped); f – ASL-perfusion (increased blood flow in the tumor); intraoperative photographs: g – in white light, h – in BLUE 400 mode (the tumor main node is brightly fluorescing), i – in white light (view of the cavity after removal of the tumor main part, speech disturbances in the form of perseverations were observed in response to electrical stimulation of the bed, the resection was stopped), j – in BLUE 400 mode (residual fluorescence of the bed in infiltration zone); postoperative MRI (T1 with contrast): k – axial section (revealed subtotal removal of the contrasted part of the tumor), l – sagittal section*

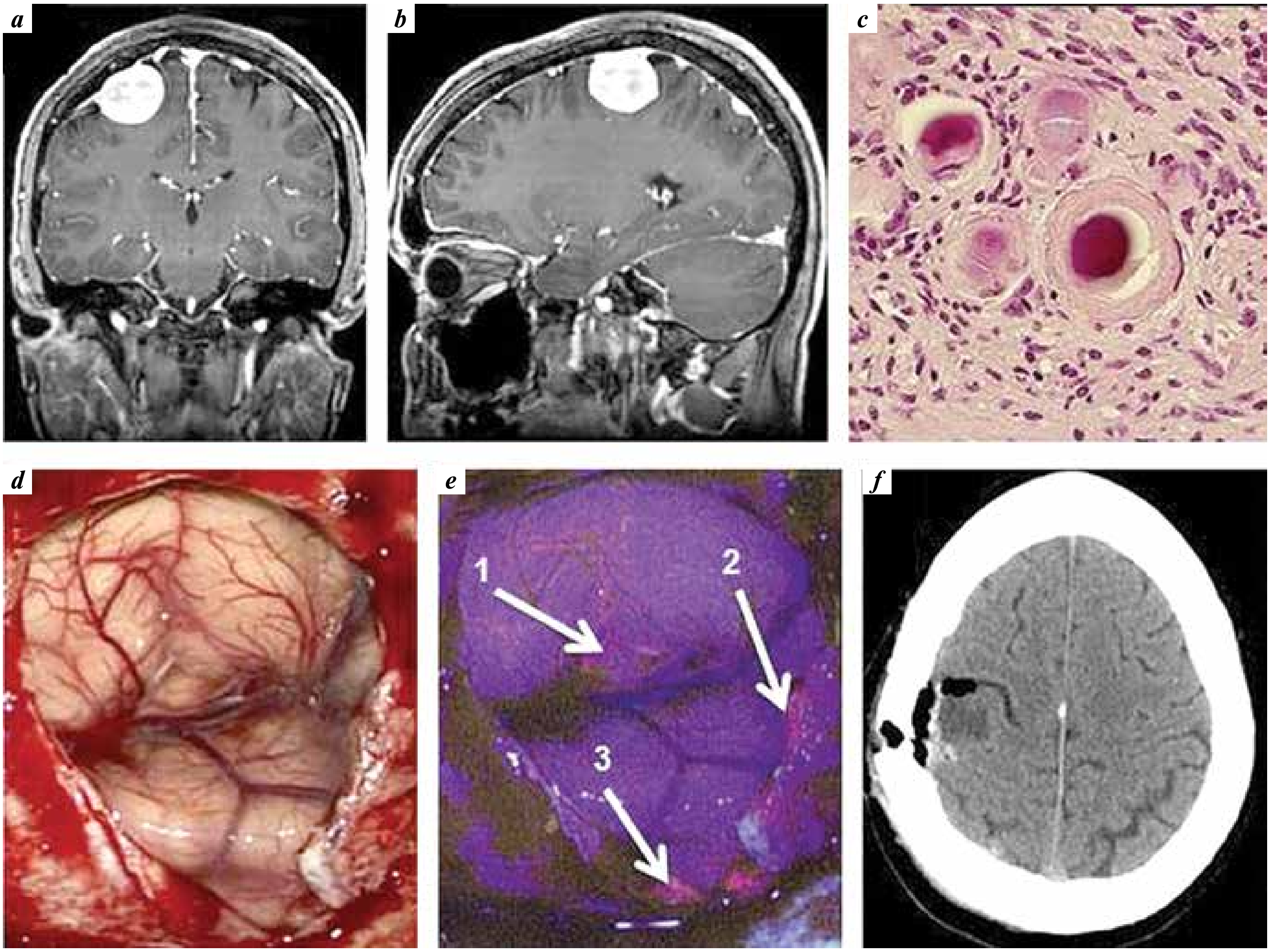

Fig. 5. *Images (patient S., 37 years old, with meningioma of the right parietal region): a, b – preoperative MRI (T1 with contrast), coronary and sagittal sections, respectively; c – histological preparation of the tumor; d, e – intraoperative photographs in white light and fluorescent mode of the BLUE 400 microscope, respectively, areas of tumor cells invasion to intima of vessels (arrow 1) and dura mater (arrows 2, 3) are visible; f – postoperative CT*

Clinical example 5

Patient M., *59 years old, with suspected lymphoma of deep parts of the right frontal lobe. In course of STB the MN was used, during biopsy sampling the patient's biopsies had bright FL (Fig. 7). Subsequent histological examination revealed a plasmocytoma.*

DISCUSSION

Initially, the MN method was used in the surgery of malignant brain GL and that practice has proved advantage of the FLD in tumor surgery as compared to classical resection in white light. Analysis of the treatment outcomes in patients having been operated with the 5-ALA has revealed statistically significant increase in overall and 6-month relapse-free survival as well as significant increase in frequency of complete resection achievement of contrast-accumulated part of the tumor [2]. In recent years, the number of publications on the use of MN in neuro-oncology has been steadily increasing. According to our data, this method has a number of advantages and disadvantages (Table 2).

As can be seen from Table 2, the FLD is a fast and convenient method of intraoperative diagnosis in neuro-oncology. According to the data obtained, the maximum sensitivity of the MN was detected in malignant GL and ICM.

There are few publications in the modern literature investigating various predictors of the FL-effect in surgery of brain GL, in particular, those employing tumor contrast [10]. However, it is not entirely clear what influence on the FL-effect have the following factors: blood flow indicators (ASL perfusion); methionine accumulation index (PET); volume of contrasted and non-contrasted tumor parts; presence or absence of an oligocomponent in the GL; treatment with anticonvulsants. According to our data, the volume of contrasting part of the GL (preoperative MRI), the methionine accumulation index (preoperative PET) and blood flow indicators in the tumor (ASL perfusion) have demonstrated the most reliable prognostic value for intraoperative FL.

According to the present study data, the FL allows to visualize both contrasting and non-contrasting tumor parts in case of malignant GL. At the same time, in white light

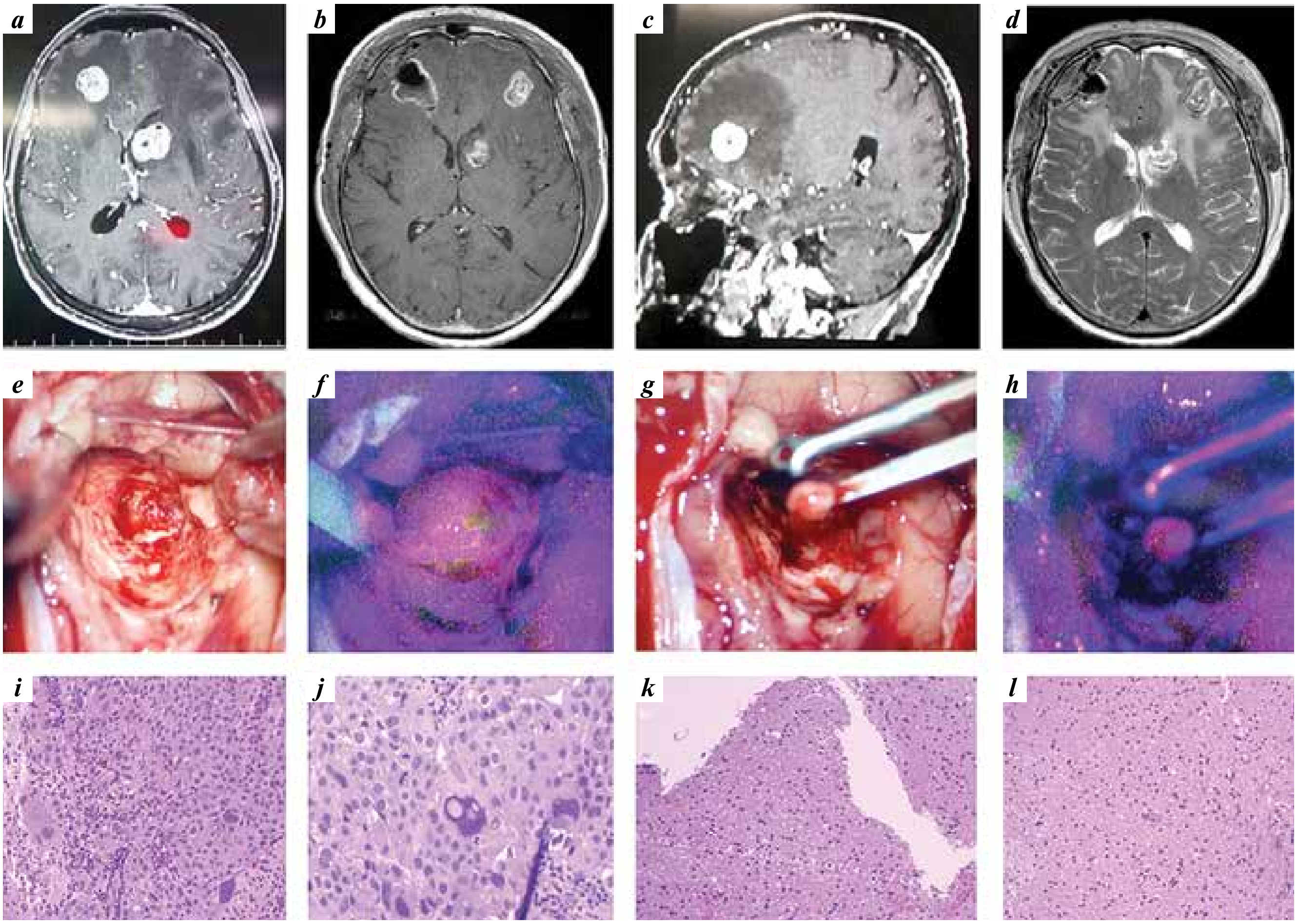

Fig. 6. *Clinical example of fluorescence in the bed of removed metastatic node in patient Zh., 60 years old; the patient had multiple nodes of the breast cancer. Additional biopsy sampling: a, b – preoperative MRI with contrast, axial sections at different levels; c – T1 with contrast, sagittal section; d – MRI (T2) in the early postoperative period; e, f – sequential visualization of intraoperative photographs in white and fluorescent microscope modes at the end of main stage of node removal; g, h – the same during sampling of additional biopsy from the bed (the bed of removed metastasis is visualized in white and blue light, a bright glow is noted), a fluorescent biopsy is in the tweezers; i, j, k, l – pathomorphological examination: i – the material of the main tumor node, k, l – the contents of fluorescent zones in the bed of removed nodes, the sample contains brain tissue while tumor tissue is not detected. Magnification: ×100 (i), ×200 (j)*

with ordinary microscope settings, the latter is often represented by an unchanged tissue in the bed.

The issue of fluorescence of low malignancy GL is debatable. In particular, a number of studies have shown a high variation in the FLD sensitivity in this category of patients: from 0 to 40 % [11, 12]. At the same time, according to some authors, the FL can detect anaplasia zones with diffuse GL of Grade II–III [10]. According to our data, the areas of luminescence in diffuse GL can both coincide in histology with the main part of non-luminous GL volume and display anaplastic foci with areas of increased density in cell nuclei and proliferative index.

Due to small number of publications on the FL use in ICM, it is necessary to clarify the need to employ the FLD method during removal of these tumors [12–14]. At the same time, the use of 5-ALA helps the surgeon to identify additional areas of glow of lesioned DM, bone structures and arachnoid matter, that is supported by the results of our study: in 36 % of cases with ICM, this method revealed additional lesions in bone structures, dura and arachnoid meninges of the brain.

In ICM surgery with the 5-ALA implementation, a pronounced variation in the method sensitivity has been reported [7, 15]. At the same time, despite the high sensitivity of the FL in relation to solid part of the tumor, the specificity of tumor cells detection in the fluorescent bed of removed metastases remains low.

The issue of the FLD method implementation in stereotactic surgery has not been resolved in the literature. There are few works on the FL use during STB [16, 17]. According to our data, the FL method has shown high efficiency in assessing *ex vivo* luminescence in lymphoma and malignant GL biopsies.

The issue of the 5-ALA use in GL surgery of brain functionally significant areas is especially difficult, in particular, the issue of combined implementation of 5-ALA navigation and surgery with intraoperative "awakening" in cases of GL localized in the brain speech areas and near long associative tracts [18].

In addition to quantitative analysis of the FL-effect, the use of spectroscopy makes it possible to perform its

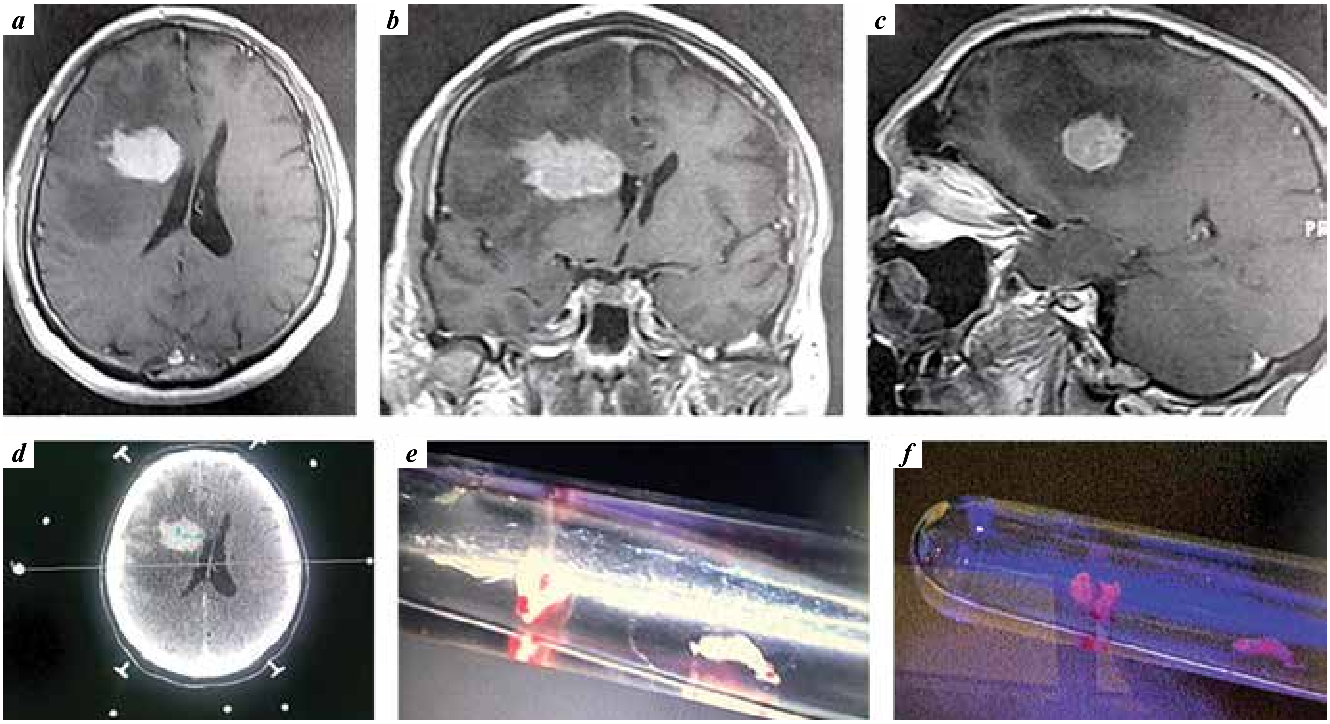

Fig. 7. *Intraoperative fluorescent diagnostics in patient M. having plasmocytoma of deep parts of the right frontal lobe. Preoperative MRI of the brain (T1 with contrast): a – axial projection, b – coronary projection, c – sagittal projection; d – intraoperative spiral computed tomography with contrast, axial section; biopsies: e – in white light, f – in fluorescent microscope mode (bright glow of the tumor)*

Table 2. *Advantages and disadvantages of metabolic navigation with 5-ALA in neuro-oncology that are common to all types of tumors*

Advantages	Disadvantages
Real-time examination	Fluorescence is not visualized: under hemostatic material or blood clotting (high optical density)
There is no effect of brain displacement	Presence of inhomogeneously weakly luminous or non-luminous tumors
Direct visualization (microscope)	Fluorescence decreases during prolonged and frequent switching of the microscope due to photobleaching ("bleaching")
Transmission of information directly from the tissue and not by the use of a "picture"	After bipolar coagulation, the glow effect is not visible under layer of coagulation scab and hemostatic materials
The possibility of multiple and rapid repetition during the surgery	
Possibility of use regardless of other methods (without other neuroimaging techniques) in the presence of bright homogeneous tumor glow	

quantitative assessment. In the available literature, there are few works on the use of spectroscopy in surgery of the brain GL [13, 19]. According to our study, the highest accumulation of PP was observed in ICM.

CONCLUSIONS

1. Metabolic navigation using microscope has shown high sensitivity during microsurgical operations (including repeated ones) with anaplastic GL (in general – 65 %, bright glow – 58 %), GL (in general – 94 %, bright glow – 53 %), ICM (in general – 94 %, bright glow – 64 %). However, the 5-ALA has significant limitations in sensitivity with diffuse GL (overall – 46 %, bright glow – 27 %) and metastases in the brain (87 % – for the solid part, 52 % – for the bed, bright glow – 51 %).
2. Metabolic navigation makes it possible to identify anaplasia foci during resection of diffuse GL (25.6 %), while the density of cell nuclei and proliferative index in fluoropositive zones of Grade II–III GL are significantly higher than in fluoronegative zones (on mean 7.41 *vs* 2.52 %). The bright FL of the tumor biopsy in STB is a reliable (83 %) predictor of the informativeness of STB.
3. During the MN, the maximum sensitivity among all brain tumors demonstrates ICM (for a solid part – 94 %, for hyperostoses – 42 %). Bright FL was observed

in 64 % of patients, moderate – in 24 %, weak – in 12 % of patients. Despite the fact that the tumor is extra-cerebral and differs well from the brain tissue in white light, the FL allows identification of areas of additional lesion of bone, dura mater and arachnoid meninges in 36 % of cases.

4. In 87 % of patients with ICMs the FL is revealed, of which 23 % have weak FL, 26 % have moderate FL, and 51 % have severe FL. The degree of luminescence of brain metastases is significantly influenced by the primary source, the time since radiosurgical exposure and the presence of intraoperative bleeding.

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