RESULTS OF MICROSURGICAL RESECTION OF GLIOBASTOMAS UNDER ENDOSCOPIC AND FLUORESCENT CONTROL

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Abstract

Overall survival and recurrence-free survival (RFS) in patients with glioblastoma directly depend on the radicality of tumor resection. According to a number of literature sources, it is known that endoscopic surgeries under fluorescence control increase the rate of total resection. However, until now, there is little data on whether endoscopic resection with fluorescence control affects RFS and overall survival of patients with glioblastoma. The aim of our study was to investigate the effect of intraoperative endoscopic and fluorescence control on overall survival and RFS in patients with glioblastoma. A retrospective single-center analysis was performed in 20 patients with glioblastoma. Ten patients underwent tumor resection using an operating microscope with endoscopic and fluorescence control. In 5 patients, 5-aminolevulinic acid (5-ALA) (alasens) at a dose of 20 mg/kg was used as a photosensitizer, in 5 patients, chlorin e6 (photoditazine) at a dose of 1 mg/kg. Ten patients underwent resection under endoscopic control, but without fluorescence control. Both cohorts of patients were comparable in age, functional status, tumor localization, adjuvant treatment methods, and molecular status. The criteria for assessing the effectiveness of the study in the groups were: the radicality of the surgical intervention according to postoperative magnetic resonance imaging with contrast enhancement, as well as the median RFS and OS in patients. In the group of combined surgery under microscopic and fluorescence control with an endoscope, the rate of total tumor resection was higher than in the group of patients who underwent only surgery under a microscope and an endoscope without fluorescence control (100% versus 60%; p = 0.002). Median OS (20.2 months (95% CI 11.9-28.6) versus 16.3 months (95% CI 11.0-20.9); (p = 0.003)) and median RFS (11.7 months (95% CI 9.8-15.7) versus 9.8 months (95% CI 6.1-13.4) (p = 0.04)), were also statistically significantly higher compared to the group of patients who received treatment to the same extent, but without fluorescence control. As our experience has shown, the use of fluorescence control during tumor resection in patients with glioblastoma with endoscopic assistance is certainly necessary, given the technical capabilities available, as it has a positive effect on the treatment results for this category of patients.

Key words: glioblastoma, endoscopy, fluorescent resection, results, survival, 5-ALA, chlorin e6.

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РЕЗУЛЬТАТЫ МИКРОХИРУРГИЧЕСКОЙ РЕЗЕКЦИИ ГЛИОБЛАСТОМ ПОД ЭНДОСКОПИЧЕСКИМ И ФЛУОРЕСЦЕНТНЫМ КОНТРОЛЕМ

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Резюме

Общая выживаемость (ОВ) и безрецидивная выживаемость (БРВ) у пациентов с глиобластомой напрямую зависит от радикальности резекции опухоли. Согласно данным ряда авторов эндоскопические операции под флуоресцентным контролем увеличивают частоту тотальной резекции. Однако до сих пор имеется мало данных о влиянии эндоскопической резекции с флуоресцентным контролем на показатели БРВ и ОВ пациентов с глиобластомой. Целью нашего исследования было изучение влияния интраоперационного эндоскопического и флуоресцентного контроля на показатели ОВ и БРВ у пациентов с глиобластомой. Проведен ретроспективный одноцентровый анализ у 20 пациентов с глиобластомой. 10 пациентам выполнена резекция опухоли с использованием операционного микроскопа с эндоскопическим и флуоресцентным контролем. У 5 пациентов в качестве фотосенсибилизатора использовали

5-аминолевулиновую кислоту (5-АЛК) в дозе 20 мг/кг, у 5 пациентов хлорин е6 в дозе 1 мг/кг. 10 пациентам выполнена резекция под эндоскопическим контролем, но без флуоресцентного контроля. Обе когорты пациентов были сопоставимы по возрасту, функциональному состоянию, локализации опухоли, методам адъювантного лечения и молекулярному статусу. Критериями оценки эффективности проводимого исследования в группах были: радикальность проведенного оперативного вмешательства по данным послеоперационной магнитно-резонансной томографии с контрастным усилением, а также медианы БРВ и ОВ. В группе комбинированного хирургического вмешательства под микроскопическим и флуоресцентным контролем с эндоскопом частота тотальной резекции опухоли была выше, чем в группе пациентов, перенесших только хирургическое вмешательство под микроскопом и эндоскопом без флуоресцентного контроля (100% против 60%; p=0,002). Медиана ОВ в первой группе составила 20,2 мес (95% ДИ 11,9-28,6) против 16,3 мес во второй группе (95% ДИ 11,0-20,9) (p=0,003), медиана БРВ 11,7 мес. (95% ДИ 9,8-15,7) против 9,8 мес (95% ДИ 6,1-13,4)% (p=0,04). соответственно. Как показал наш опыт, использование флуоресцентного контроля во время резекции опухоли у пациентов с глиобластомой при эндоскопической ассистенции положительно отражается на результатах лечения пациентов с глиобластомой и может быть рекомендовано для широкого внедрения в клиническую практику.

Ключевые слова: глиобластома, эндоскопия, флуоресцентная резекция, результаты, выживаемость, 5-АЛК, хлорин е6.

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Despite recent advances in neurooncology and the development of new treatment methods [1–5], the survival rate of patients with glioblastoma remains low [6, 7]. The median overall survival (OS) in this category of patients ranges from 11 to 17 months [6, 7]. Surgical resection is an important step in the treatment of patients with glioblastoma [8]. It has been proven that the use of fluorescence guidance during surgical intervention in patients with glioblastoma increases the OS and RFS rates, which is confirmed by convincing results of prospective randomized neurosurgical studies [9–15].

The main goal of surgical treatment is the complete removal of tumor tissue while maximally preserving the patient's neurological functions. A number of studies have shown that the totality of resection significantly increases the RFS and OS medians compared to subtotal resection in patients with glioblastoma [15–20]. In turn, visualization of fluorescence may be difficult due to the collapse of the edges of the post-resection cavity and a decrease in illumination with an increase in the depth of the resection cavity [10, 12, 14]. This may lead to limitations in microscopic resection under fluorescence control: visible fluorescence of tumor tissue depends on the cell density and cellular metabolism, as well as on adequate exposure of the tumor tissue to blue light [16, 18 – 20].

Several scientific papers have demonstrated that the use of an endoscope with fluorescence control made it possible to increase the degree of resection radicality, and according to data from individual publications, to improve the OS rates in patients with malignant brain tumors [21 – 26]. Information on the use of a combined approach (endoscope and fluorescence) is quite limited, which actualizes the significance of our study. There are also few literature data assessing the impact of fluorescence-guided and endoscope-guided resection of glioblastoma on OS and RFS rates in patients [22, 24–30].

Materials and methods

The study was a retrospective single-center analysis of the effectiveness of fluorescence endoscopic control in the removal of primary glioblastomas in patients [31] who underwent routine microscopic resection under endoscopic control in the period from 2014 to 2016 at the Russian Neurosurgical Research Institute named after prof. A.L. Polenov. The patients were assessed for resection totality, RFS, and OS rates.

Of the 20 patients in both groups, 13 (65%) were men and 7 (35%) were women. The average age was 56.0 years, 4 (20%) patients were over 65 years old.

All 20 patients underwent preoperative MRI with gadolinium contrast enhancement. All patients underwent a preoperative clinical and diagnostic examinations, including examination by specialists (neurologist, therapist, oncologist, ophthalmologist) and laboratory and instrumental research methods (blood and urine tests, electroencephalogram, electrocardiogram). Detailed clinical characteristics of patients in both groups are presented in Table 1.

The study protocol was reviewed by the local ethics committee (Protocol No. 4 dated 17/12/2013). All patients were informed about the course of the surgery. Written consent was obtained from all patients as part of the standard informed consent procedure for surgery.

Inclusion and Exclusion Criteria

Only patients with primary glioblastoma, the localization of which was clearly defined, were included in the study to ensure that the totality of resection could be achieved in all patients. Patients were over 18 years old. Patients who underwent biopsy or required intraoperative neuromonitoring were excluded. Patients without postoperative contrast-enhanced MRI of the brain, patients in severe condition, patients with signs of renal and hepatic insufficiency, chronic viral infections

(hepatitis C, B, HIV infection), and patients with endocrine diseases or metabolic disorders were also excluded.

Surgical stage

Of the 10 patients in the main group, 5 patients received 5-ALA (alasens) as a fluorescence inducer orally, manufactured by the Scientific Center "NIOPIK", Federal State Unitary Enterprise (Russia), at a dose of 20 mg/kg, 8 hours before the intraoperative stage of the operation. Tumor removal was performed using an intraoperative microscope with fluorescence control (OPMI Pentero 800, Carl Zeiss, Germany).

Five patients of the main group received intravenous fluorescence inducer chlorin e6 (photoditazine), manufactured by OOO VETA-GRAND (Russia), at a dose of 1 mg/kg, dissolved in 200 ml of 0.9% sodium chloride solution, 2 hours before the expected stage of

Таблица 1
Клиническая характеристика пациентов
Table 1
Clinical characteristics of patients

Признак / Sign	Эндоскопический контроль / Endoscopic control	Эндоскопический и флуоресцентный контроль / Endoscopic and fluorescent control	Значение p / p value
Количество пациентов / Number of patients	10	10	
Возраст / Age			
Границы / Age limits	33-73	41-68	0,8
Медиана / Median age	55,6	56,5	
Пол / Gender			
мужчины / men	7 (70%)	6 (60%)	0,7
женщины / women	3 (30%)	4 (40%)	
Предоперационный индекс Карновского / Preoperative Karnofsky index			
Границы / Index boundaries	70-100	70-100	0,9
Медиана / Median	85	83	
Предоперационный размер опухоли, см³ / Preoperative tumor size, cm³			
Медиана / Median	25,4	27,8	0,7
Границы / Size limits	3,4-37	4,2-44,5	
Преимущественная локализация опухоли / Predominant tumor location			
лобная доля / frontal lobe	3 (30%)	2 (20%)	0,6
теменная доля / parietal lobe	2(20%)	4 (40%)	
височная доля / temporal lobe	4(40%)	4 (40%)	
затылочная доля / occipital lobe	1 (10%)	0 (0%)	
Полушарие / Hemisphere			
правое / right	7 (70%)	4 (40%)	0,01
левое / left	3 (30%)	6 (60%)	
Характер опухоли по данным МРТ головного мозга с контрастным усилением гадолинием / Character of the tumor according to MRI of the brain with gadolinium contrast enhancement			
кистозное / cystic	2 (20%)	1 (10%)	0,8
кистозно-солидное / cystic-solid	7 (70%)	8 (80%)	
солидное / solid	1 (10%)	1 (10%)	
MGMT метилирование после первой операции / MGMT methylation after first surgery			
положительный / positive	4 (40%)	3 (30%)	0,7
отрицательный / negative	6 (60%)	7 (70%)	

the operation. Tumor removal was performed using an operating microscope (LEICA OHS–1) with the D-Light AF System Karl Storz (Germany) and a fluorescence attachment manufactured by Russia Science Seoul, Korean Electrotechnology Research Institute (KERI), (Seoul, Republic of Korea) (developed by G.V. Papayan).

Tumor removal in the group without fluorescence control was performed under the control of an intraoperative microscope (OPMI Pentero, Carl Zeiss, Germany).

For endoscopic control, an endoscope (Karl Storz, Germany) with a special light source (D-light C; Karl Storz) and a camera system (Karl Storz) were used in all patients in both groups. The endoscope was used after complete microscopic removal of all visualized tissue.

For the fluorescence control group, the endoscope was set to the D-light mode, which allowed switching between white and blue light source modes using a corresponding bandpass filter in the light transmission path (Fig. 1). A long-pass filter on the endoscope eyepiece blocked excitation light, which allowed detection of tumor cell fluorescence signals. The excitation and detection filter system allowed transmission of enough blue light so that the red fluorescence of endogenous fluorophores and non-specific fluorescence were suppressed, resulting in normal tissue being visualized as blue. Microscopic fluorescent tissue and endoscopic fluorescent tissue not visualized under the microscope were completely removed and used separately for histopathological examination (Fig. 2).

Postoperative evaluation

All patients underwent MRI within 24 h after surgery. Any residual enhancement greater than 0.2 cm^3 was defined as residual tumor. Performance status was assessed using the Karnofsky scale at discharge. All included patients underwent regular clinical examination and contrast-enhanced MRI every 3 months. The presence of recurrence was assessed by subsequent MRI according to the Response Assessment in Neuro-Oncology (RANO) criteria [8].

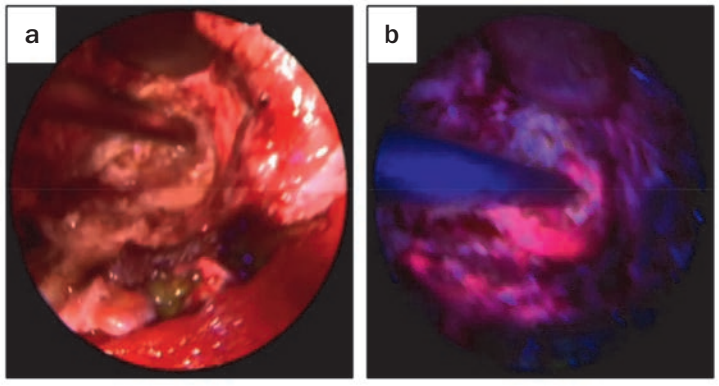

Рис. 1. Интраоперационная картина:
a – изображение в эндоскопе при обычном освещении, без флуоресценции;
b – изображение в эндоскопе в флуоресцентном режиме.
Fig. 1. Intraoperative picture:
a – endoscope view under normal lighting, without fluorescence;
b – endoscope view in fluorescent mode.

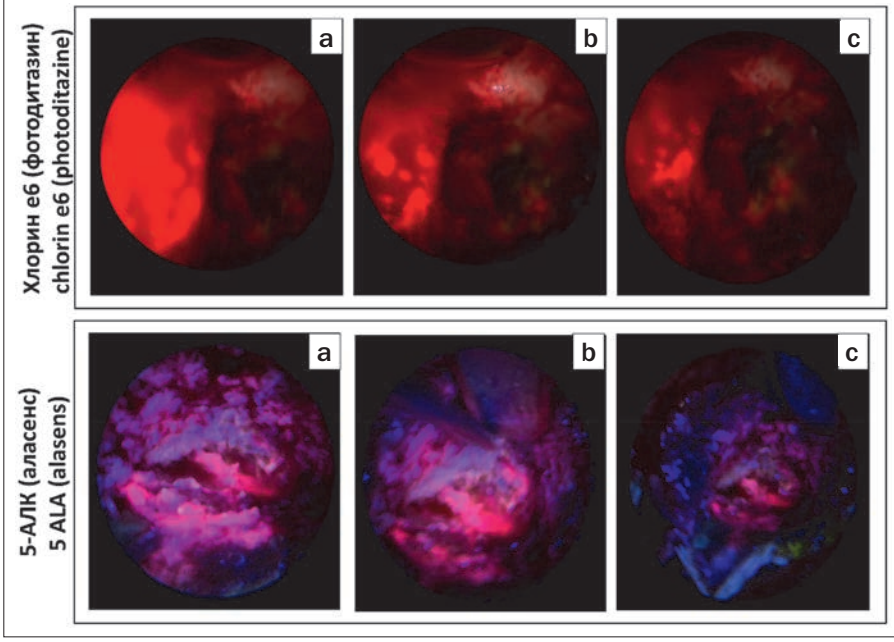

Рис. 2. Интраоперационная картина флуоресцентной диагностики в процессе резекции опухоли 5-АЛК и хлорином е6 (a, b, c – поэтапное удаление части опухолевой ткани накопившей флуоресцент).
Fig. 2. Intraoperative picture of fluorescent diagnostics during tumor resection with 5-ALA and chlorin e6 (a, b, c – step-by-step removal of part of the tumor tissue that has accumulated fluorescence).

Postoperative period

All patients received standard adjuvant therapy (chemotherapy and radiotherapy) in the postoperative period according to the Stupp protocol [32]. Radiotherapy included fractionated external beam therapy to the resected tumor bed with a total focal dose of 50-60 Gy in 25-30 fractions (1.8-2.0 Gy per fraction), for 5-6 weeks. As chemotherapy after the first operation, patients received temozolomide (at a dose of 150-200 mg/m^2 from the 1st to the 5th day every 28 days).

In the postoperative period, patients underwent control MRI of the brain every 3 months in the first 12 months or when symptoms appeared, then every 4 months.

If a relapse was detected based on MRI of the brain, if indicated, repeated surgical treatment was performed or the patient was referred for repeated adjuvant therapy (chemotherapy and radiation therapy). Chemotherapy regimens for relapse were prescribed by oncologists based on the results of histological examination of the tumor material, after repeated surgeries, or according to generally accepted regimens. The following chemotherapy regimens were used: avastin + irinotecan; PCV (lomustine, vincristine, procarbazine); lomustine + vincristine; temozolomide + avastin.

Efficacy assessment criteria of the conducted study

The efficacy assessment criteria of the conducted study in the groups were: radicality of the performed surgical intervention according to the data of postoperative MRI with contrast enhancement and values of the OS and RFS medians.

Statistical analysis

All analyses were performed using SPSS (version 20, IBM Corp.). Continuous variables were measured as mean or median values and standard deviation. Differences between both cohorts were analyzed using the unpaired

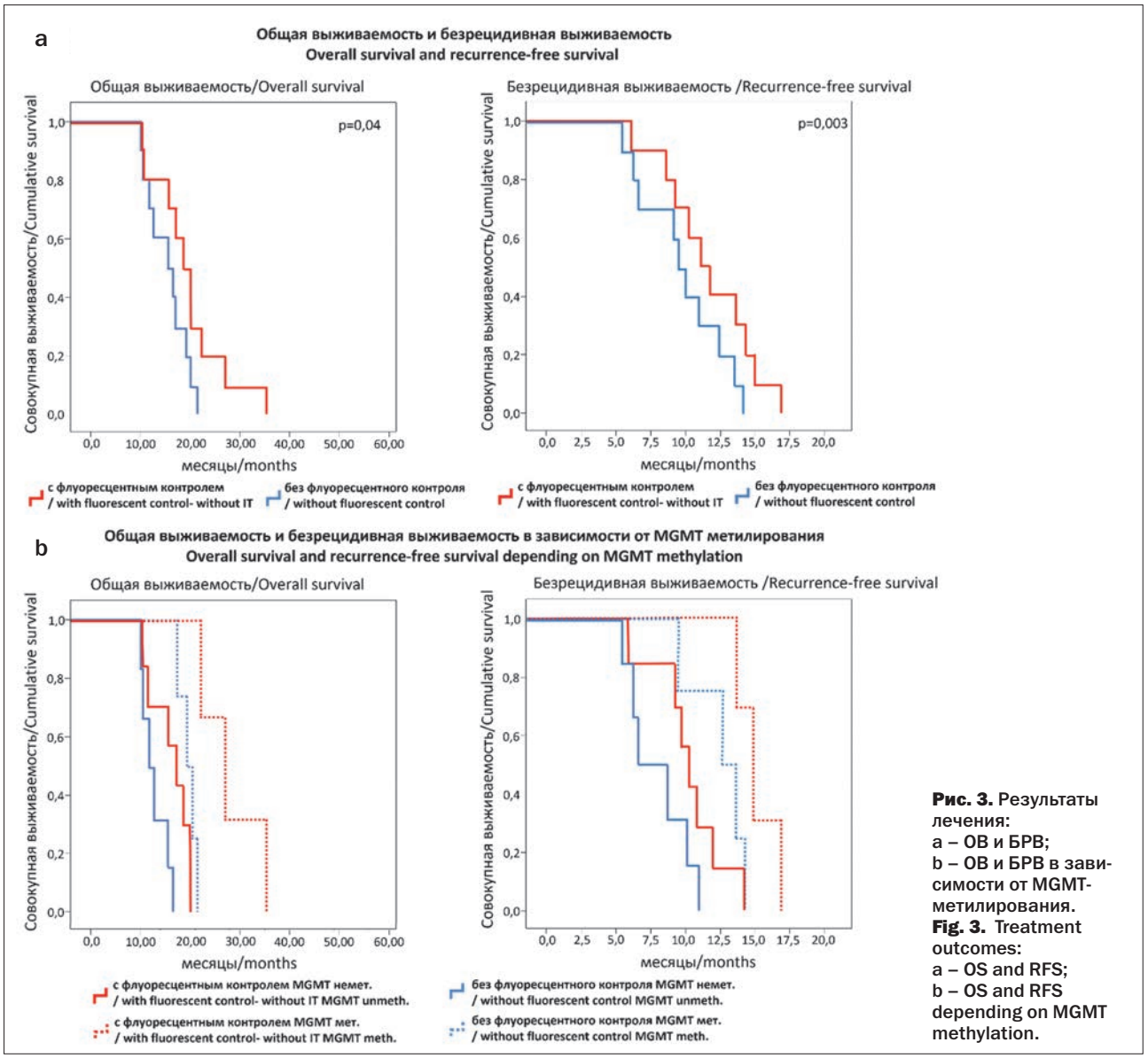

Рис. 3. Результаты лечения:
a – ОВ и БРВ;
b – ОВ и БРВ в зависимости от MGMT-метилирования.
Fig. 3. Treatment outcomes:
a – OS and RFS;
b – OS and RFS depending on MGMT methylation.

t-test. Descriptive survival was analyzed using the Kaplan-Meier method, p-values < 0.05 were considered significant.

Results

In the early postoperative period, no patient experienced complications associated with endoscopic or fluorescence control during surgery. The Karnofsky index values in patients in each group after surgery were comparable with preoperative data (p=0.9).

Totality of resection, RFS, and OS

According to postoperative gadolinium-enhanced MRI of the brain, total resection was achieved in all 10 (100%) patients who underwent combined surgery under a microscope and fluorescence control with an endoscope, compared with 6 (60%) patients who underwent only surgery under a microscope and an endoscope without fluorescence control (p=0.002). The RFS median in the cohort of combined resection using fluorescence control with an endoscope and a microscope was 11.7 months. (CI 95% 9.8–15.7) versus 9.8 months (CI 95% 6.1–13.4; p=0.04) in the cohort of resections using a microscope and endoscope, but without fluorescence control (Fig. 3a).

The OS median in the cohort of combined resection with fluorescence and endoscopic control and a microscope was 20.2 months (CI 95% 11.9–28.6) compared with 16.3 months (CI 95% 11.0–20.9) in the cohort of resection using a microscope and endoscope, but without fluorescence control (p=0.003) (Table 2, Fig. 3a).

A direct connection was shown between the detection of a number of molecular markers, in particular the MGMT methylation index, and the RFS and OS rates. Thus, according to our study, patients in both groups with a methylated MGMT promoter had better OS and RFS rates compared with patients with an unmethylated MGMT promoter (Fig. 3b).

In our study, no relationship was found between age, gender, preoperative Karnofsky index, tumor location and size before surgery, volume of adjuvant therapy (chemotherapy and radiotherapy), and the values of RFS and OS. This is partly due to the fact that the patients who were selected for the study were maximally comparable in these characteristics, partly due to the small sample of patients.

Таблица 2
Результаты лечения пациентов в зависимости от клинических и гистологических данных

Table 2
Treatment results for patients depending on clinical and histological data

Пациент / Patient	Резекция с флуоресцентным контролем / Fluorescence-guided resection	Пол / Gender	Возраст / Age	Индекс Карновского / Karnofsky index KPS	Локализация опухоли (доля/сторона) / Tumor Location (lobe/side)	Характер опухоли по данным МРТ головного мозга с контрастным усилением гадолинием / Character of the tumor according to MRI of the brain with gadolinium contrast enhancement	Размер опухоли (см³) / Tumor volume (cm³)	MGMT метилирование / MGMT methylation	IDH мутация / IDH mutation	Тотальность резекции по данным МРТ / Totality of resection according to MRI data	Повторная резекция / Repeated resection	Общая доза ЛТ (Гр) / Total dose of RT (Gr)	Количество циклов ТМЗ / Number of TMZ cycles	Безрецидивная выживаемость, мес. / Recurrence-free survival, months	Вторая/третья линия лечения после рецидива / Second/third line of treatment after relapse	Общая выживаемость, мес. / Overall survival, months
1	да/yes	ж/f	45	90	лобная правая/frontal right	кистозно-солидное/cystic-solid	33,1	мет/meth	нет/no	да/yes	да/yes	60	8	17,1	ТМЗ+авастин/TMZ+avastin	36,5
2	да/yes	м/m	68	90	теменная левая/parietal left	кистозно-солидное/cystic-solid	4,2	мет/meth	IDH1 (R132H)	да/yes	да/yes	60	6	13,5	ТМЗ/TMZ	22,4
3	да/yes	ж/f	61	100	лобная левая/frontal left	солидное/solid	29,6	немет/unmeth	нет/no	дда/yes	нет/no	60	5	8,8	авастин+ иринотекан/avastin+ irinotecan	11,5
4	да/yes	м/m	57	80	височная левая/temporal left	кистозно-солидное/cystic-solid	10,8	немет/unmeth	IDH1/IDH2	да/yes	да/yes	60	7	14,5	ТМЗ/TMZ	20,3

5	да/yes	ж/f	49	80	теменная правая/parietal right	кистозно-солидное/cystic-solid	37,1	немет/unmeth	нет/no	да/yes	да/yes	90	6	10,7	ТМЗ+авастин/TMZ+avastin	17,7
6	да/yes	ж/f	58	80	теменная левая/parietal left	кистозно-солидное/cystic-solid	42	мет/meth	нет/no	да/yes	да/yes	60	6	15,3	ТМЗ/TMZ	27,9
7	да/yes	м/m	41	70	височная левая/temporal left	кистозное/cystic	38,7	немет/unmeth	нет/no	да/yes	нет/no	60	5	11,8	ТМЗ/TMZ	20,3
8	да/yes	ж/f	60	70	височная правая/temporal right	кистозно-солидное/cystic-solid	44,5	немет/unmeth	нет/no	да/yes	нет/no	60	3	9,3	ломустин + винкристин/lomustine + vincristine	18,4
9	да/yes	м/m	67	90	теменная правая/parietal right	кистозно-солидное/cystic-solid	20,6	немет/unmeth	нет/no	да/yes	да/yes	60	7	10,1	PCV (ломустин, винкристин, прокарбазин)/PCV	16,6
10	да/yes	ж/f	59	80	височная левая/temporal left	кистозно-солидное/cystic-solid	17,4	немет/unmeth	нет/no	да/yes	да/yes	90	5	5,8	ломустин + винкристин/lomustine + vincristine	10,7
11	нет/no	ж/f	58	70	лобная правая/frontal right	кистозно-солидное/cystic-solid	35,5	немет/unmeth	нет/no	нет/no	нет/no	60	3	6,4	ТМЗ+авастин/TMZ+avastin	11,9
12	нет/no	ж/f	44	90	теменная правая/parietal right	кистозно-солидное/cystic-solid	29,7	мет/meth	нет/no	нет/no	нет/no	90	6	13,8	авастин+ иринотекан/avastin+ irinotecan	22,3
13	нет/no	м/m	46	90	височная правая/temporal right	кистозно-солидное/cystic-solid	37	немет/unmeth	нет/no	да/yes	да/yes	60	5	11,1	PCV (ломустин, винкристин, прокарбазин)/PCV	17,6
14	нет/no	м/m	69	90	теменная левая/parietal left	солидное/solid	18,8	немет/unmeth	нет/no	да/yes	да/yes	60	7	10,2	ТМЗ/TMZ	16,9
15	нет/no	ж/f	73	80	височная правая/temporal right	кистозное/cystic	28,5	немет/unmeth	нет/no	нет/no	нет/no	60	5	8,3	ТМЗ+авастин/TMZ+avastin	13,3
16	нет/no	ж/f	61	90	лобная левая/frontal left	кистозно-солидное/cystic-solid	33,9	мет/meth	нет/no	да/yes	нет/no	60	7	9,8	ТМЗ/TMZ	18,9
17	нет/no	ж/f	55	70	височная правая/temporal right	кистозно-солидное/cystic-solid	29,8	немет/unmeth	IDH1 (R132H)	нет/no	да/yes	60	9	5,3	ТМЗ/TMZ	11,1
18	нет/no	ж/f	60	80	височная левая/temporal left	кистозно-солидное/cystic-solid	17,6	мет/meth	нет/no	да/yes	да/yes	60	5	14,6	авастин+ иринотекан/avastin+ irinotecan	20,1
19	нет/no	м/m	57	100	затылочная правая/occipital right	кистозное/cystic	3,4	немет/unmeth	нет/no	да/yes	да/yes	45	6	6,1	ТМЗ+авастин/TMZ+avastin	10,5
20	нет/no	ж/f	33	90	лобная правая/frontal right	кистозно-солидное/cystic-solid	19,4	мет/meth	нет/no	да/yes	да/yes	60	5	12,5	ломустин + винкристин/lomustine + vincristine	17,7

Morphological analysis

Morphological examination of tumor areas depending on fluorescence intensity showed that there is a direct connection between tumor cell density, tumor anaplasia degree, and fluorescence intensity during surgery. The brighter the tumor tissue fluorescence, the higher the tumor cell density, and the more malignant the tumor area according to morphology (Ki-67 and TP 53 index, VEGF expression level). In the tumor necrosis zone, either very weak fluorescence or no fluorescence was observed. The sensitivity of the fluorescence monitoring method during surgery (dependence of fluorescence intensity on

tumor anaplasia degree) was 100%, and the specificity (when comparing fluorescent and non-fluorescent tumor tissue areas) reached 85% (Fig. 4).

Comparison of the morphological data of biopsies obtained during surgery in patients for whom 5-ALA and chlorin e6 were used as fluorescence inducers did not show a significant difference in the specificity and sensitivity of detecting tumor tissue areas.

Morphological analysis of tumor tissue areas in patients in the group with endoscopic control, but without fluorescence control, showed that the sensitivity of the technique for detecting tumor tissue areas was 60% (analysis of possible areas perceived as tumor tissue, taken during surgery under visual endoscopic control), and the specificity was 40% (comparative analysis between tissue areas taken during surgery that were perceived under endoscopic control as tumor tissue, and areas that were perceived in the endoscopic picture as normal brain tissue).

Discussion

In this study, we assessed the effect of fluorescence guidance in combined microscopic and endoscopic resection on median RFS and OS medians in patients with glioblastoma. The sensitivity and specificity of the techniques were also assessed. Our results indicate that median RFS and OS were higher in patients with glioblastoma if endoscopic resection was supplemented with fluorescence guidance. Thus, the use of fluorescence guidance allowed increasing the sensitivity of the technique from 60 to 100%, and the specificity from 40 to 85%.

Effect of a combined approach on resection radicality

Analysis of different works shows that the use of an endoscope during surgery allows the surgeon to significantly increase the frequency of total resections (95%) and achieve a significantly greater removal of tumor tissue volume, not limited to the contrasting parts of the tumor according to MRI data [18, 25]. And the use of fluorescence control in addition to the endoscope allows for the radicality of resection to be brought to a higher level [26–28, 30, 33]. In addition, the use of a combination of an endoscope and fluorescence control in glioblastoma removal appears to be a safe and feasible technique, since an endoscope in fluorescence mode allows for the identification of tumor tissue with high sensitivity (100%) and specificity (85%) [27, 28]. Due to a significant decrease in the distance between the light source and the tumor tissue, endoscopic control and fluorescence control make it possible to identify tumor tissue that is not sufficiently visualized microscopically (located at the edges of the tumor, in blind zones around the craniotomy area, and deep in the surgical field with poorer illumination). This, in turn, leads to an increase in the frequency of total resections and makes it possible to perform supratotal resection [26, 30].

Thus, in the work of A.A. Potapov et al. [23], 17 patients underwent microsurgical resection with fluorescence

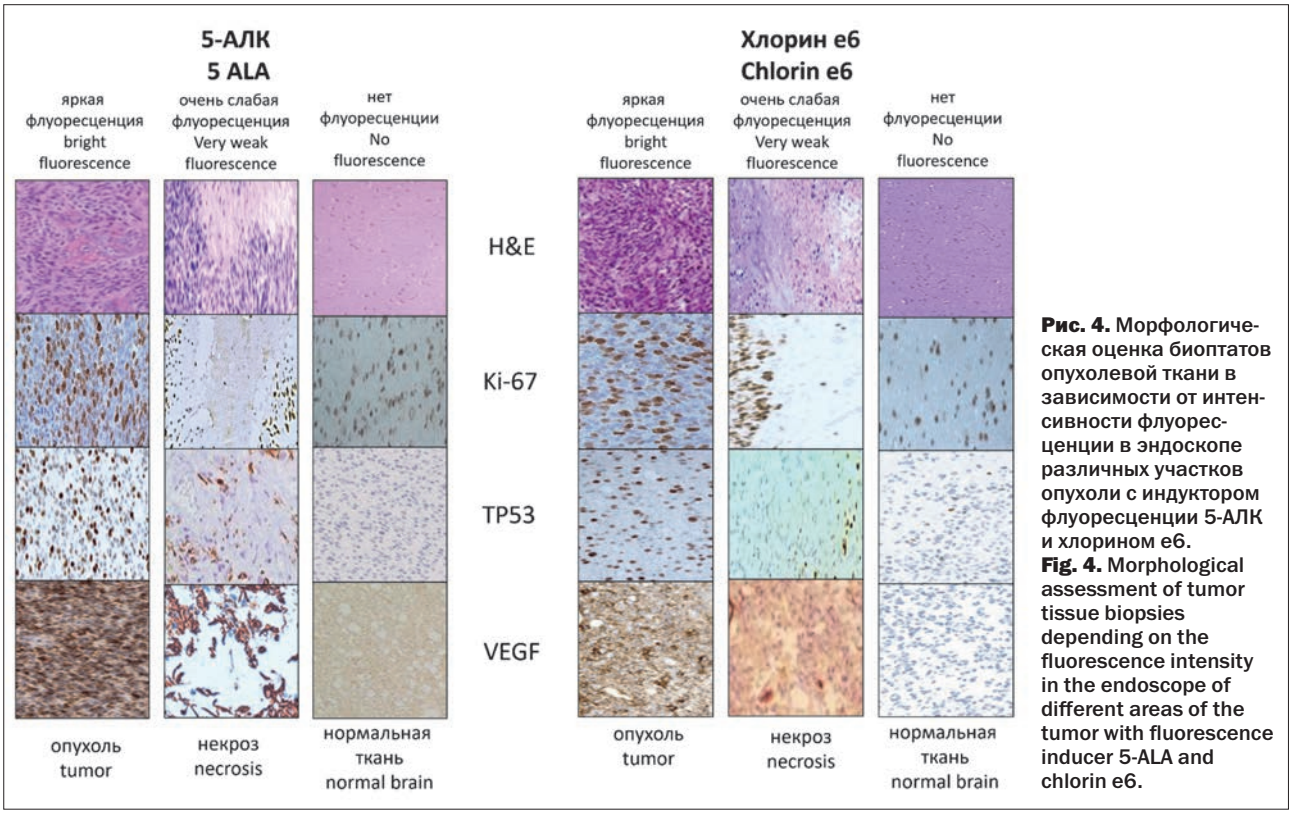

Рис. 4. Морфологическая оценка биоптатов опухолевой ткани в зависимости от интенсивности флуоресценции в эндоскопе различных участков опухоли с индуктором флуоресценции 5-АЛК и хлорином е6.
Fig. 4. Morphological assessment of tumor tissue biopsies depending on the fluorescence intensity in the endoscope of different areas of the tumor with fluorescence inducer 5-ALA and chlorin e6.

endoscopy using 5-ALA and Karl Storz endoscopic equipment to determine tumor residues in the resection cavity. The primary diagnosis of the tumor included malignant gliomas, metastases, and malignant tumors of the skull base. In most cases, the possibility of monitoring the " out of the border " areas of the resection cavity using an angled endoscope was confirmed. Bright fluorescence was observed not only in grade IV gliomas, but also in 3 of 4 metastases. The authors concluded that the use of an endoscope to perform fluorescence navigation with 5-ALA increases the diagnostic efficiency for differentiating normal brain tissue from tumor tissue [23].

Our results further highlight the importance of endoscopic and fluorescence guidance in glioblastoma resection and demonstrate that the current limitations of standard endoscopically guided surgery can be overcome by adding fluorescence guidance.

Impact on overall survival

In the study by Bettag et al. [24], additional fluorescence and endoscopic guidance were used during surgery in 20 of 114 patients, while the remaining patients underwent tumor resection under the control of an operating microscope and fluorescence. Both cohorts were comparable in age, functional status, lesion location, adjuvant treatment methods, and molecular status. Complete total resection was achieved in all patients treated with the use of endoscopy, compared with approximately 75.9% of patients treated with the use of only a microscope (p=0.003). The RFS median in the cohort using an endoscope was 19.3 months. (95% CI 10.8–27.7) compared with 10.8 months (95% CI 8.2–13.4; p=0.012) in the microscope-only cohort. The OS median in the endoscope group was 28.9 months (95% CI 20.4–34.1) compared with 16.8 months (95% CI 14.0–20.9) in the microscope-only group (p=0.001) [24].

Our study showed that the use of endoscopic and fluorescence guidance increased the resection completeness rate and thereby improved RFS and OS rates in patients with glioblastoma.

Study Limitations

Our study has several limitations. First, it was a retrospective study and further prospective studies are needed to confirm our results. Second, the cohort in which the combined approach was used was small and selective. Third, the entire study population was selective since only patients with well-localized glioblastomas were included in the study. However, both cohorts were comparable in terms of potential confounding factors, which allows to suggest that the combined approach is superior to the standard microscopic approach with an endoscope in terms of the radicality rate of the performed surgery and survival in patients with glioblastoma.

Conclusion

This is one of the first studies in our country comparing fluorescence-guided glioblastoma resection using an endoscope with standard resection using an endoscope in addition to microscopic resection. The use of fluorescence guidance during tumor resection using an endoscope, as shown by our experience, increases the radicality of resection and the OS and RFS medians in patients with glioblastoma. At the same time, it should be noted that the observed effect contrasts with the limitations of the study design. Therefore, there is a need to continue conducting further research on a larger group of patients to confirm our findings.

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