FLUORESCENT DIAGNOSTICS WITH CHLORIN e6 IN SURGERY OF LOW-GRADE GLIOMA

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Abstract

Intraoperative fluorescence diagnostics of high-grade gliomas is widely used in neurosurgical practice. This work analyzes the possibilities of fluorescence diagnostics for low-grade gliomas (LGG) using chlorin e6 photosensitizer. The study included patients with newly diagnosed LGG, for whom chlorin e6 was used for intraoperative fluorescence control at a dose of 1 mg/kg. During the operation, the fluorescence intensity of various areas of the putative tumor tissue was analyzed using the RSS Cam – Endo 1.4.313 software. Tissue samples with various degrees of fluorescence intensity were compared with the results of their histopathological analysis (WHO tumor diagnosis, Ki-67 index, P53, VEGF). Fluorescence was detected in more than half of the cases, but in most cases had a focal character and low fluorescence intensity. The fluorescence intensity directly correlated with the data of histopathological examination of tumor tissues (Ki-67 index (p=0.002), expression of P53 (p=0.0015) and VEGF (p=0.001)). The sensitivity of the method for LGG surgery was 72%, the specificity was 56,7%. Intraoperative fluorescence diagnostics with chlorin e6 can be used in LGG surgery, especially to visualize intratumoral areas with a higher degree of anaplasia.

Key words: low-grade gliomas, chlorin e6, intraoperative fluorescence diagnostics, neurooncology.

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ФЛУОРЕСЦЕНТНАЯ ДИАГНОСТИКА С ХЛОРИНОМ e6 В ХИРУРГИИ ГЛИОМ НИЗКОЙ СТЕПЕНИ ЗЛОКАЧЕСТВЕННОСТИ

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Резюме

Применение интраоперационной флуоресцентной диагностики для глиом высокой степени злокачественности широко используется в нейрохирургической практике. В работе проанализированы возможности флуоресцентной диагностики для глиом низкой степени злокачественности с использованием хлорина e6. В исследование были включены пациенты с впервые диагностированной глиомой низкой степени злокачественности (low-grade glioma, LGG), у которых с целью интраоперационного флуоресцентного контроля применен препарат хлорин e6 в дозе 1 мг/кг массы тела. В процессе операции анализировали интенсивность флуоресценции различных участков предполагаемой опухолевой ткани с использованием программного обеспечения RSS Cam – Endo 1.4.313. Образцы тканей различной степени интенсивности флуоресценции сопоставляли с результатами их гистопатологического анализа (диагностика опухоли ВОЗ, индекс Ki-67, P53, VEGF). Флуоресценция выявлена в более чем половине случаев, но в большинстве случаев имела очаговый характер и низкую интенсивность флуоресценции. Интенсивность флуоресценции напрямую коррелировала с данными гистопатологического исследования тканей опухоли: индекс Ki-67 (p=0,002), экспрессия P53 (p=0,0015), VEGF (p=0,001). Чувствительность метода для хирургии LGG составила 72%, специфичность 56,7%. Проведенное исследование подтвердило, что технология интраоперационной флуоресцентной диагностики с применением хлорина e6 может применяться в хирургии LGG, особенно для визуализации внутриопухолевых участков с более высокой степенью анаплазии.

Ключевые слова: глиомы низкой степени злокачественности, хлорин e6, интраоперационная флуоресцентная диагностика, нейроонкология.

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Introduction

Low-grade gliomas (LGGs) are a heterogeneous group of astrocytic and oligodendroglial tumors and account for about 20% of all newly diagnosed brain tumors, with an incidence of 5.2 cases per 100,000 people per year. The mean survival of patients with LGG ranges from 5 to 13 years. This wide range of LGG survival rates is most likely due to differences in clinical, histopathological, and molecular genetic factors. Age and clinical status, histopathological, molecular genetic (1p19q co-deletion, isocitrate dehydrogenase (IDH) mutation status, O^6-methylguanine methyltransferase promoter methylation status (MGMT)) and other factors play an important role in predicting the course of the disease in patients [1– four].

LGGs present a particular challenge for the neurosurgeon during surgery due to the histopathological heterogeneity of the tumor and the lack of a clear tumor margin. The goal of surgical intervention in LGG is to perform resection of the neoplasm to the maximum extent, but allowing to preserve neurological functions and create conditions for an optimal prognosis of the course of the disease. Therefore, new methods are needed to overcome this surgical problem [1, 3, 4]. Intraoperative imaging of brain tumors using fluorescence is one of the major advances in neurosurgery over the past decades. Initially, this method was used exclusively for surgery of high-grade gliomas (HGG) [5–8]. In recent years, the use of fluorescence has been extended to other cases, such as neuroimaging suspicion of LGG on MRI (CT) or PET [3, 7, 9, 10].

Commonly used modern neuronavigation systems (MRI spectroscopy, diffusion-weighted MRI, perfused-weighted MRI, PET using amino acids) lack accuracy when performing glioma resection due to the so-called "brain shift", leading to significant inaccuracies in image management, since neuronavigation is based on preoperative image data. The occurrence of brain shift during surgery with suspected LGG may preclude accurate detection of the tumor margin and anaplastic lesion. Insufficient intraoperative identification of LGG tissue, as well as insufficient differentiation of intratumoral HGG focal tissue, which is an anaplastic lesion in LGG tissue, are a serious problem for the neurosurgeon. As a result, incomplete resection is observed in 88% of cases with surgical intervention for LGG, and histopathological inaccuracy in postoperative diagnosis is not uncommon in routine neurosurgical practice [4, 6, 7, 9, 11].

Intraoperative imaging of brain tumor tissue using fluorescence is one of the most effective methods for visualizing tumor tissue during surgery [5, 6, 8, 13]. An analysis of modern literature sources has shown that there are very few works that have published the results of using fluorescence in LGG surgery [6, 7, 11, 14, 15].

In this study, we present our experience of using fluorescent navigation in LGG surgery using a medicinal product from the e6 chlorin group as a photosensitizer.

Materials and methods

The study involved 7 patients with LGG operated at the Russian Research Neurosurgical Institute named after prof. A.L. Polenova. All patients underwent fluorescent navigation with chlorin e6 during tumor resection in case of suspected newly diagnosed LGG. According to the postoperative pathohistological examination, two pilocytic astrocytomas (PA), two fibrillar protoplasmatic astrocytoma (FPA), two oligoastrocytomas (OA), and one oligodendroglioma (ODG) were diagnosed. There were 4 men in the study, 3 women (see table).

Preoperative neuroimaging assessment in all patients was performed according to MRI of the brain with gadolinium contrast enhancement using a Siemens apparatus (1.5 T) and PET with methionine. A mandatory criterion for inclusion of a patient in the study was the possibility of removing more than 90% of the tumor tissue according to the expected MRI data with contrast. To calculate the tumor volume from MRI data, the diameters at right angles were measured in the axial, frontal, and sagittal planes. The calculation was carried out according to the modified ellipsoidal volume according to the formula MER=A+B+C/2, where A, B, and C are the orthogonal values of the tumor.

Before surgery, all patients gave informed written consent to the administration of chlorin e6. No side effects associated with the use of 2nd generation chlorin e6 (photoditazine, produced by VETA-GRAND LLC, Russia) were noted in the study.

2 hours before the proposed durotomy, the patient was intravenously injected with the medicinal product chlorin e6 at the rate of 1 mg/kg of body weight, dissolved in 200 ml of isotonic solution. The vial with 0.9% sodium chloride solution was previously closed from the outside with an opaque material. During the operation, a modified neurosurgical microscope (Leica OHS-1) Karl Storz (Germany) with a built-in fluorescent module manufactured by LOMO (Saint-Petersburg, Russia) was used. During the operation, to visualize fluorescent tissue areas, the microscope was constantly switched to the fluorescent mode.

The fluorescence intensity was assessed using special software RSS Cam – Endo 1.4.313, which makes it possible to measure the fluorescence intensity in a given place in real time in numerical terms (Fig. 1A). The fluorescence intensity was distributed on a scale from 0 to 9 points depending on the numerical indicator in the software, where 0 is the complete absence of

Таблица
Клиническая характеристика пациентов
Table
Clinical characteristics of the patients

№п\п Sequential number	Пол Sex	Возраст Age	Доля мозга Lobe of the brain	Предоперационный индекс Карновского Preoperative Karnofsky index	Размеры опухоли (по данным МРТ), см^3 Tumor size (according to MRI data), cm^3	ПЭТ с метионином (индекс накопления РФП) PET with methionine (RP accumulation index)	Гистология Histology	Стадия Grade
1	М M	41	левая височная left temporal	80	5,5	0,15	пилоцитарная астроцитома pilocytic astrocytoma	I
2	Ж F	55	правая лобная right frontal	80	4,3	0,11	пилоцитарная астроцитома pilocytic astrocytoma	I
3	М M	45	левая височная и теменная left temporal and parietal	90	6,1	0,7	фибриллярно-протоплазматическая астроцитома fibrillar-protoplasmic astrocytoma	II
4	Ж F	60	правая лобная right frontal	70	3,7	0,91	фибриллярно-протоплазматическая астроцитома fibrillar-protoplasmic astrocytoma	II
5	М M	33	правая височная right temporal	80	6,3	0,78	олигоастроцитома oligoastrocytoma	II
6	Ж F	29	левая височная left temporal	80	4,9	0,93	олигоастроцитома oligoastrocytoma	II
7	М M	47	правая лобная и височная right frontal and temporal	90	6,7	0,55	олигодендроглиома oligodendroglioma	II

fluorescence, 9 is a bright red intense glow. During the operation, a biopsy was performed from fluorescent and non-fluorescent areas of the tumor. A total of 80 biopsy samples with different fluorescence intensities were examined.

The biopsy material obtained during the operation was fixed in 10% buffered formalin, dehydrated and embedded in paraffin. Next, sections 3 μm thick were stained with hematoxylin-eosin.

Immunohistochemical (IHC) markers were also detected, in particular, Ki-67 (MIB-1), p53 (TP53), and VEGF (vascular endothelial growth factor) (Fig. 1Д). The paraffin blocks were sectioned 3-5 μm thick, deparaffinized using xylene, and rehydrated with various concentrations of ethanol. Sections were dried in a thermostat at 45°C. The standard IHC protocol was used with antigen demasking in a water bath (GFL, 1002), using primary antibodies from Dako (Ki-67, Clone Mib-1, cat. no. M7240; P53, Clone DO-7, cat. no. M7001; VEGF, Clone VC1, cat. no. M7273) and imaging systems from Diagnostic BioSystems (UMR1000PD-BMS).

The Ki-67 proliferation index was determined by the percentage of cells with immunoreactive nuclei to the total number of cells. According to WHO (2016),

these parameters are as follows: G I – 1-3%, G II – 4-5%, G III – 5-10%, G IV – an average of 15-20% and above.

For the IHC study of P53, monoclonal antibodies DO-7 were used, which detect both wtP53 and mtP53. It is believed that the IHC response depends mainly on the presence of mtP53 in the tissue, since wtP53 is a short-lived protein with a half-life of no more than 20 min, and its content may be below the sensitivity of the IHC study. The half-life of mtP53 lasts up to 24 hours, so the level of its accumulation in the tissue is sufficient for visualization. To quantify the proliferative activity, as well as the expression of the P53 protein, the ratio of stained nuclei per 300 cells was calculated at a magnification of 400 times. Conditionally, the following gradation was adopted: no expression (0 points); weak expression (1 point) – less than 10% of cell nuclei are stained; moderate expression (2 points) – more than 10% of the nuclei are stained, but less than 33%; strong expression (3 points) – more than 33% of cell nuclei in the tissue are positive. The color of more than 5% of cell nuclei was considered as the control level.

The expression level of VEGF was estimated as % of the control level (0.4 ng/ml), the measurement was carried out in ng/mg.

Subsequently, intraoperative fluorescence data were compared with the data obtained from the results of histopathological examination.

Statistical analysis was performed using the STATISTICA 13.0 software package (StatSoft, USA). When correlating non-binary variables such as Ki-67 (MIB-1), p53 (TP53), VEGF, histological subtype with fluorescence intensity categorical variables, the Mann-Whitney U-test was used. Statistical analysis of other data was performed using non-parametric methods using Spearman's rank correlation coefficient. Differences were considered statistically significant at $p<0.05$.

Results

Visual fluorescence was obtained in 4 out of 7 patients. In 2 observations, fluorescence had a focal character, in 2 cases it was homogeneous. Fluorescence was further studied using the RSS Cam–Endo 1.4.313 software (Fig. 1A). Out of 50 biopsies with varying fluorescence intensity, about 26% were false positives according to the software, which was confirmed by histopathological examination. But, despite this, the sensitivity of the technique in detecting tumor sites was high (Fig. 1Б) (p=0.002).

When studying the distribution of fluorescence intensity in areas of tumor tissue depending on the WHO histological classification of tumors of the central nervous system (2016), it was found that ODG (Grade II) was characterized by a greater number of intense fluorescence regions and a more developed vascular network. The smallest number of fluorescence sites was characteristic of PA (Grade I), in addition, they were characterized by the largest number of false positive fluorescence sites in the analysis of biopsy material (Fig. 1B). Pronounced development of the vascular network was characteristic of FPA.

In the study of the relationship between the fluorescence intensity of LGG tumor tissue areas and the data of their histopathological examination (Ki-67, P53, VEGF), a direct correlation was obtained. The higher the fluorescence intensity, the higher the Ki-67 nuclear expression index (p=0.002), the higher the level of transcription factor of the cell cycle protein P53 (p=0.002), the higher the level of VEGF expression (p=0.001) (Fig. 2). A stronger correlation was between fluorescence intensity and VEGF expression (p=0.001) (Fig. 2C).

A study of the sensitivity and specificity of the fluorescent navigation method for LGG surgery, based on the evaluation of histopathological data from fluorescent and non-fluorescent biopsy specimens, showed that the sensitivity of the method was 72% (36/50), the specificity was 56.7% (13/30) (p= 0.003).

Clinical example

A 45-year-old patient was admitted with a diagnosis of a mass lesion in the left temporal and parietal lobes of the brain. From the anamnesis it is known that he has been ill for a year, when he began to notice the following symptoms: headache, difficulty in pronouncing words, convulsions. The neurologist sent for an MRI of the brain with contrast enhancement. A volumetric formation of the left temporal and parietal lobes was revealed, evenly accumulating a contrast agent with a moderate change in the architectonics of the gyri. According to PET-CT of the brain with methionine, the accumulation index of the radiopharmaceutical agent (RPC) is 0.7.

During the operation, the method of fluorescent diagnostics with a preparation of the chlorin e6 group (photoditazine) was used. A microscope Leica-OHS1 with a fluorescent module developed by LOMO (St. Petersburg) was used. During the removal of the tumor in the fluorescent mode, a red glow (5–6 points) was noted, homogeneous in all areas of the altered tissue. Histopathological examination revealed fibrillar-protoplasmatic astrocytoma (Grade II) (Fig. 3).

Discussion

In the study of Goryainov S.A. et al. [3], which included 27 patients with morphologically confirmed LGG, of which 14 were diagnosed with diffuse astrocytoma, 6 with ODG, 4 with PA, 2 with gemistocytic astrocytoma, 1 with desmoplastic ganglioglioma, visible fluorescence of 5-aminolevulinic acid (5 -ALK) was detected in 14 (52%) patients. According to the homo-

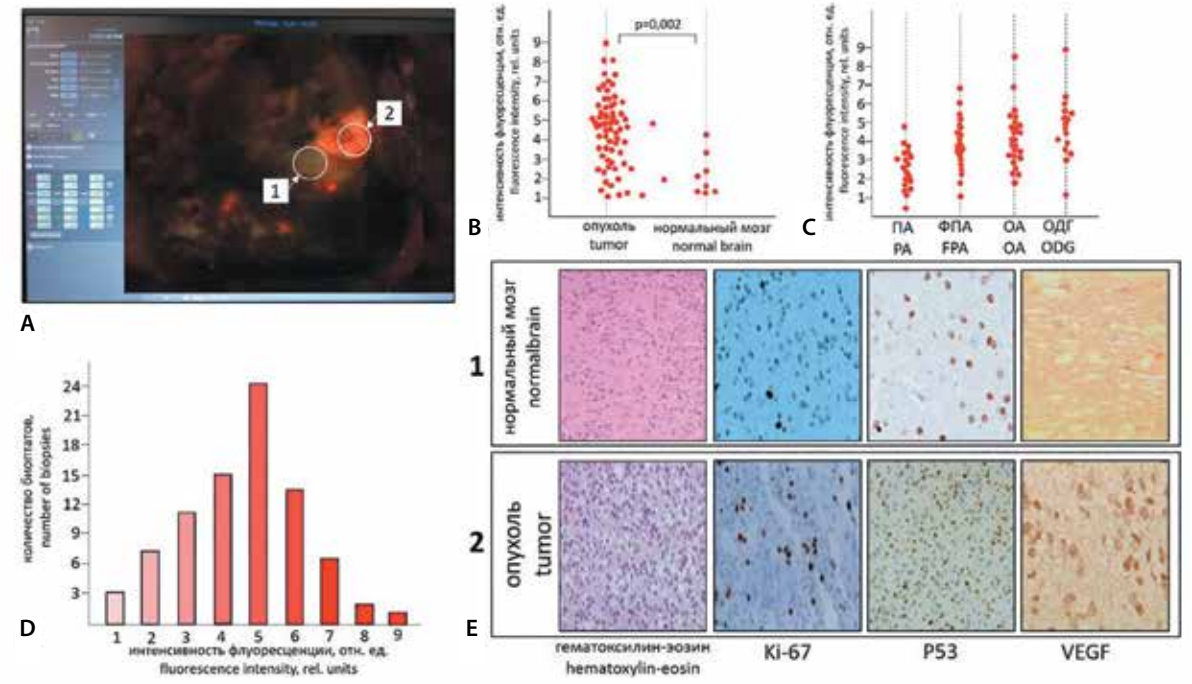

Рис. 1. Анализ интенсивности флуоресценции участков опухолевой ткани. А – анализ флуоресценции участков ткани с использованием программного обеспечения RSS Cam – Endo 1.4.313; В – зависимость между интенсивностью флуоресценции биоптата и результата гистологического исследования (опухоль – неизмененная мозговая ткань) (p=0,002); С – распределение интенсивности флуоресценции в участках опухолевой ткани в зависимости от гистологической классификации опухоли по данным ВОЗ (ПА – пилоцитарная астроцитома, ФПА – фибриллярно-протоплазматическая астроцитома, ОА – олигоастроцитома, ОДГ – олигодендроглиома); D – график распределения интенсивности флуоресценции в отобранных биоптатах; Е – гистопатологическое исследование участков опухоли в зависимости от интенсивности флуоресценции.

Fig. 1. Analysis of the intensity of fluorescence of areas of tumor tissue. A – analysis of the fluorescence of tissue sites using the RSS Cam Endo 1.4.313 software; B – the relationship between the fluorescence intensity of the biopsy specimen and the result of histological examination (tumor – unchanged brain tissue (normal brain)) (p=0,002); C – distribution of fluorescence intensity in areas of tumor tissue depending on the histological classification of the tumor according to WHO data (PA – pilocytic astrocytoma, FPA – fibrillar-protoplasmic astrocytoma, OA – oligoastrocytoma, ODG – oligodendroglioma); D – graph of the distribution of fluorescence intensity in the selected biopsy specimens; E – histopathological examination of tumor sites depending on the intensity of fluorescence.

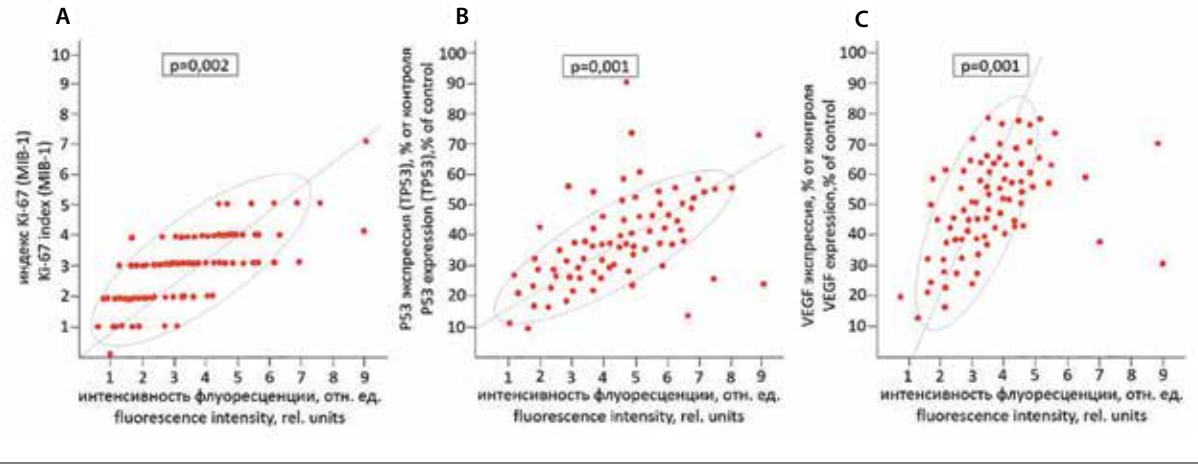

Рис. 2. Зависимость между интенсивностью флуоресценции участков опухолевой ткани и индексом ядерной экспрессии Ki-67 (MIB-1) (А); экспрессией транскрипционного фактора клеточного цикла P53 (TP53) (В) и VEGF (С).

Fig. 2. Dependence between the intensity of fluorescence of tumor tissue sites and the index of Ki-67 nuclear expression (MIB-1) (A); cell cycle transcription factor P53 (TP53) expression (B) and VEGF expression (C).

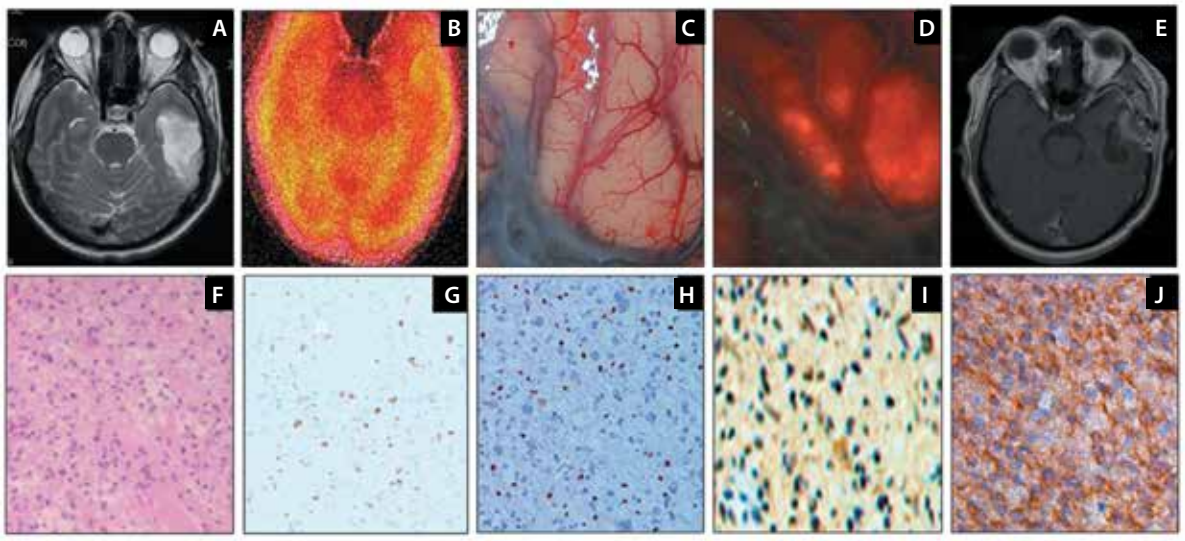

Рис. 3. Фибриллярно-протоплазматическая астроцитома левой теменной и височной долей головного мозга.
A – предоперационное МРТ головного мозга с контрастом (Т2-режим);
B – ПЭТ с метионином (индекс накопления РФП – 0,7);
C – интраоперационная картина без флуоресцентного режима;
D – интраоперационная картина, полученная во флуоресцентном режиме с хлорином е6;
E – послеоперационное МРТ,
F – фибриллярно-протоплазматическая астроцитома. Окрашивание гематоксилин-эозином. Иммуногистохимия. Ув. 200;
G – экспрессия белка пролиферативной активности Ki-67= 9. Иммуногистохимия. Ув. 200;
H – экспрессия транскрипционного фактора клеточного цикла P53 (+). Иммуногистохимия. Ув. 200;
I – экспрессия транскрипционного фактора Olig 2. Иммуногистохимия. Ув. 200;
J – экспрессия VEGF (+). Иммуногистохимия. Ув. 400.

Fig. 3. Fibrillar-protoplasmic astrocytoma of the left parietal and temporal lobes.
A – preoperative MRI of the brain with contrast (T2-mode);
B – PET with methionine (index of RP accumulation – 0.7);
C – intraoperative picture without fluorescence mode;
D – intraoperative picture in fluorescent mode with chlorin e6;
E – postoperative MRI;
F – hematoxylin-eosin (magnification 200);
G – Ki-67 protein expression (index of proliferative activity – 9). Immunohistochemistry. (magnification 200);
H – cell cycle transcription factor P53 (+) expression. Immunohistochemistry. (magnification 200);
I – transcription factor Olig 2 expression. Immunohistochemistry. (magnification 200);
J – VEGF (+) expression. Immunohistochemistry. (magnification 400).

geneity of fluorescence, 7 tumors showed diffuse fluorescence, 7 gliomas showed focal fluorescence. Cell density and proliferation rate were significantly higher in positive fluorescent samples than in negative fluorescent samples.

Jaber M. et al. [9] found fluorescence in 16 (21.6%) LGG patients out of 74. Fluorescence was partly associated with weak enhancement on MRI and increased radiopharmaceutical uptake on PET-CT, and was not related to Karnofsky score, tumor size, or patients' age. With regard to molecular markers, only increased EGFR expression differed slightly (in 19% in fluorescent tumors, versus 5% in non-fluorescent ones (p=0.057). The median of the relapse-free period was shorter in fluorescent tumors and amounted to 46.4 months (95% CI 41.8-51.1 months). At the same time, IDH status and the presence of fluorescence were directly dependent on the duration of the period before malignant transformation of the tumor and overall survival.

When working with 5-ALA Ji S.Y. et al. [4] also recorded fluorescence in Grade I–II gliomas. Fluorescence was detected in 5 out of 9 patients with PA, in 3 cases of strong intensity, in 2 – weak. All PA could be completely removed regardless of the positive fluorescence. Out of 87 patients with Grade II gliomas, ODG predominated (57.5%, n=50). The majority of ODG showed no fluorescence (82.0%). However, there were

9 cases of fluorescence with a positive result (18.0%), including 2 cases with high intensity (4.0%). Out of 20 patients with diffuse astrocytic gliomas and OA, fluorescence was absent in 18 cases, and focal fluorescence was observed in 2 cases. Total resection was achieved in 15 patients, including those with positive fluorescence.

In an additional study published in 2017, Saito K. et al. [16] evaluated the relationship between 5-ALA fluorescence and proliferation rate, as well as molecular markers, including IDH1 mutation status and 1p19q co-deletion in a series of anaplasia grade II gliomas. Univariate analysis showed that 5-ALA fluorescence was significantly associated with proliferation rate, as well as IDH1 mutation status and 1p19q co-deletion. According to multivariative analysis, only IDH1 status remained a statistically significant factor. Gliomas with visible 5-ALA fluorescence showed a significantly higher incidence of wild-type IDH1 tumors.

T. Tsurubuchi et al. [17] used chlorin e6 (talaporfin sodium) in LGG surgery. The scientists observed strong fluorescence in a patient with PA, although only 1 case was studied. In patients with ODG with a large volume of the vascular bed of the tumor, they also managed to reliably fix fluorescence during a morphological study.

In the work of J. Akimoto et al. [18], studying intraoperative fluorescence using the photosensitizer chlorin e6 (talaporfin sodium), a weak fluorescence intensity in all patients with Grade II gliomas was revealed. The average concentration of chlorin e6 in tissues was 1.62 μg/g in areas with strong fluorescence, 0.67 μg/g with weak fluorescence and 0.19 μg/g without fluorescence.

In general, fluorescent diagnostics is of limited use in Grade I–II glioma surgery and can be used to a greater extent for visualization of anaplastic areas of the tumor. The sensitivity of the method, according to different authors, varies from 20 to 58% [3, 5, 14, 15, 19, 20]. Fluorescence can serve as a marker for the onset of malignant transformation and is an independent marker in contrast to known prognostic factors. LGG fluorescence can be taken into account when choosing adjuvant therapy [3, 19].

In our study, we obtained a high sensitivity of the fluorescent navigation technique in LGG surgery (72%), which is most likely due to a small sample of patients, and creates the need for further study of this issue. However, the specificity of the technique (56.7%) is comparable with the data obtained by a number of other authors [3, 9, 12, 17, 18].

Conclusion

The use of intraoperative fluorescent navigation with chlorin e6 in the treatment of patients with low-grade gliomas provides the doctor with additional information about the structure of the tumor in a particular patient, which allows the neurosurgeon to individualize the approach to surgical tactics during surgery. Further research in this direction seems promising in terms of determining the volume of resected tissues, which allows maintaining the ablasticity of the intervention and does not adversely affect the patient's quality of life.

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