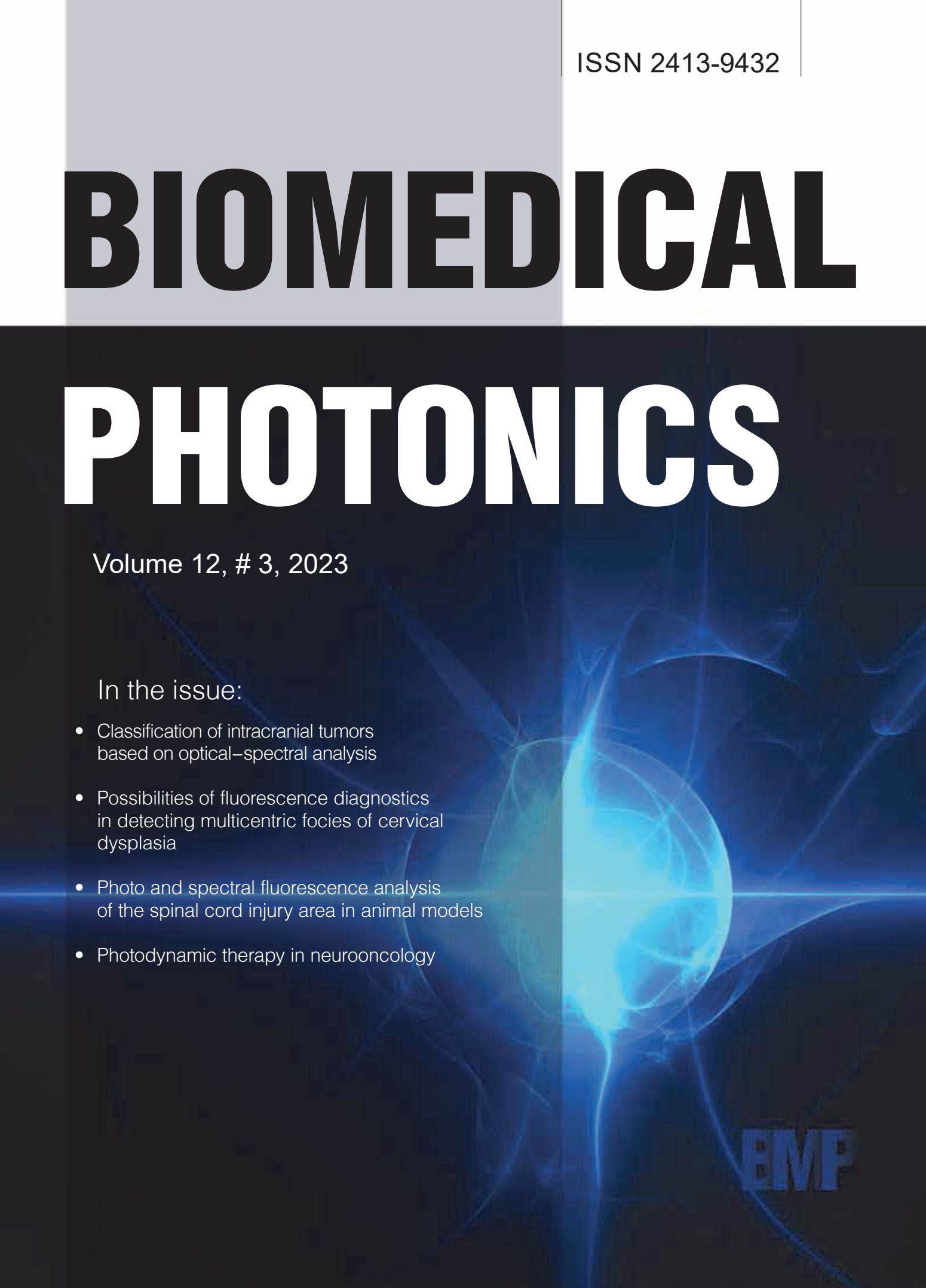
ISSN 2413-9432

BIOMEDICAL PHOTONICS

Volume 12, # 3, 2023

In the issue:



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BIOMEDICAL PHOTONICS

BIOMEDICAL PHOTONICS –
research and practice, peer-reviewed, multidisciplinary journal.
The journal is issued 4 times per year.
The circulation – 1000 copies., on a quarterly basis.

The journal is included into the List of peer-reviewed science press of the State Commission for Academic Degrees and Titles of Russian Federation
The journal is indexed in the international abstract and citation database – Scopus.

The publisher «Agentstvo MORE».
Moscow, Khokhlovskiy lane., 9

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Registration certificate ПИ № ФС 77–51995, issued on 29.11.2012 by the Federal Service for Supervision of Communications, Information Technology, and Mass Media of Russia

The subscription index of «Rospechat» agency – 70249

BIOMEDICAL PHOTONICS

BIOMEDICAL PHOTONICS –
научно-практический, рецензируемый,
мультидисциплинарный журнал.
Выходит 4 раза в год.
Тираж – 1000 экз., ежеквартально.

Входит в Перечень ведущих рецензируемых научных журналов ВАК РФ.
Индексируется в международной реферативной базе данных Scopus.

Издательство «Агентство МОРЕ».
Москва, Хохловский пер., д. 9

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Свидетельство о регистрации ПИ
№ ФС 77–51995, выдано 29.11.2012 г.
Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор)

Индекс по каталогу агентства «Роспечать» – 70249

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ORIGINAL ARTICLES

CLASSIFICATION OF INTRACRANIAL TUMORS BASED ON OPTICAL-SPECTRAL ANALYSIS

Romanishkin I.D.[1], Savelieva T.A.[1,2], Ospanov A.[2], Linkov K.G.[1], Shugai S.V.[3], Goryajnov S.A.[3], Pavlova G.V.[3,4], Pronin I.N.[3], Loschenov V.B.[1,2]
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Abstract

The motivation for the present study was the need to develop methods of urgent intraoperative biopsy during surgery for removal of intracranial tumors. Based on the experience of previous joint work of GPI RAS and N.N. Burdenko National Medical Research Center of Neurosurgery to introduce fluorescence spectroscopy methods into clinical practice, an approach combining various optical-spectral techniques, such as autofluorescence spectroscopy, fluorescence of 5-ALA induced protoporphyrin IX, diffuse reflection of broadband light, which can be used to determine hemoglobin concentration in tissues and their optical density, Raman spectroscopy, which is a spectroscopic method that allows detection of various molecules in tissues by vibrations of individual characteristic molecular bonds. Such a variety of optical and spectral characteristics makes it difficult for the surgeon to analyze them directly during surgery, as it is usually realized in the case of fluorescence methods – tumor tissue can be distinguished from normal with a certain degree of certainty by fluorescence intensity exceeding a threshold value. In case the number of parameters exceeds a couple of dozens, it is necessary to use machine learning algorithms to build a intraoperative decision support system for the surgeon. This paper presents research in this direction. Our earlier statistical analysis of the optical-spectral features allowed identifying statistically significant spectral ranges for analysis of diagnostically important tissue components. Studies of dimensionality reduction techniques of the optical-spectral feature vector and methods of clustering of the studied samples also allowed us to approach the implementation of the automatic classification method. Importantly, the classification task can be used in two applications – to differentiate between different tumors and to differentiate between different parts of the same (center, perifocal zone, normal) tumor. This paper presents the results of our research in the first direction. We investigated the combination of several methods and showed the possibility of differentiating glial and meningeal tumors based on the proposed optical-spectral analysis method.

Keywords: optical spectroscopy, intracranial tumors, machine learning.

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For citations: Romanishkin I.D., Savelieva T.A., Ospanov A., Linkov K.G., Shugai S.V., Goryajnov S.A., Pavlova G.V., Pronin I.N., Loschenov V.B. Classification of intracranial tumors based on optical-spectral analysis, *Biomedical Photonics*, 2023, vol. 12, no. 3, pp. 4–10. doi: 10.24931/2413–9432–2023–12-3-4–10.

КЛАССИФИКАЦИЯ ВНУТРИЧЕРЕПНЫХ ОПУХОЛЕЙ НА ОСНОВЕ ОПТИКО-СПЕКТРАЛЬНОГО АНАЛИЗА

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Резюме

Мотивацией проведения настоящего исследования послужила необходимость развития методов срочной интраоперационной биопсии при проведении операций по поводу удаления внутричерепных опухолей. На основании опыта предыдущей совместной работы

ИОФ РАН и НМИЦ нейрохирургии им. Н.Н. Бурденко по внедрению в клиническую практику методов флуоресцентной спектроскопии был разработан подход, комбинирующий различные оптико-спектральные методики, такие как спектроскопия аутофлуоресценции, флуоресценции 5-АЛК индуцированного протопорфирина IX, диффузного отражения широкополосного излучения, по которому можно определять концентрацию гемоглобина в тканях и их оптическую плотность, спектроскопия комбинационного рассеяния, являющаяся методом молекулярной спектроскопии, позволяющим детектировать различные молекулы в тканях за счета колебаний отдельных характерных связей в молекулах. Такое разнообразие оптико-спектральных характеристик затрудняет их непосредственный анализ хирургом во время операции, как это обычно реализуется в случае флуоресцентных методов – по превышению некоторого порога интенсивности флуоресценции с определенной степенью достоверности можно судить о том, находится ли в зоне исследования нормальная или опухолевая ткань. В случае, если число параметров превышает пару десятков, необходимо использование алгоритмов машинного обучения для построения системы поддержки принятия решений хирурга во время операции. Настоящая работа представляет исследования в этом направлении. Проведенный нами ранее статистический анализ данных оптико-спектральных характеристик позволил выделить статистически значимые спектральные диапазоны для анализа, репрезентирующие диагностически важные компоненты тканей. Исследования методов понижения размерности вектора оптико-спектральных признаков и методов кластеризации исследуемых образцов также позволили приблизиться к реализации метода автоматической классификации. Важно отметить, что задача классификации может быть использована в двух приложениях – для дифференциации различных опухолей и для дифференциации различных частей одной (центр, перифокальная зона, норма) опухоли. В настоящей работе представлены результаты наших исследований в первом направлении. Мы исследовали сочетание нескольких методов и показали возможность дифференциации глиальных и менингеальных опухолей на основании предложенного метода оптико-спектрального анализа.

Ключевые слова: оптическая спектроскопия, внутричерепные опухоли, машинное обучение.

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Для цитирования: Романишкин И.Д., Савельева Т.А., Оспанов А., Линьков К.Г., Шугай С.В., Горяйнов С.А., Павлова Г.В., Пронин И.Н., Лощенов В.Б. Классификация внутричерепных опухолей на основе оптико-спектрального анализа // Biomedical Photonics. – 2023. – Т. 12, № 3. – С. 4–10. doi: 10.24931/2413–9432–2023–12–3-4–10.

Introduction

Brain tumors are a group of neoplasms arising from various cells of the central nervous system (CNS) or from systemic cancers that have metastasized to the CNS. Systemic cancers most prone to metastasize to the CNS include lung cancer, melanoma, and breast cancer. Primary brain tumors include a number of histologic types with notably different rates of tumor growth. Brain tumors can cause symptoms associated with local invasion of the brain, compression of neighboring structures, and increased intracranial pressure.

Determination of tumor type is required at all stages of treatment for treatment planning and prognosis. One of the most common methods for automating the diagnosis of intracranial tumors is classification based on proton magnetic resonance spectroscopy data [1]. The approach based on MRI image analysis is also widely used to build automatic classification systems [2]. However, the capabilities of this method are limited and there is still a high demand for intraoperative techniques for rapid determination of tissue type in the resection area, especially such techniques are relevant for intraoperative photodynamic therapy, which is gaining popularity in neurosurgical practice [3, 4]. Optical spectroscopy methods based on both 5-ALA induced protoporphyrin IX fluorescence analysis [5–7] or chlorin-based photosensitizers [8] and molecular spectroscopy methods [9, 10] offer a wide range of possibilities in this field. We have previously proposed a combined approach integrating fluorescence and diffuse reflectance spectroscopy [11], and have further developed it by adding analysis of spontaneous Raman spectra [12, 13].

One of the important advantages of using Raman spectroscopy is that there is no need to introduce special markers into the body, since this method is based on the analysis of changes in the vibrational energy of the molecules that make up biological tissues. Therefore, the very molecular composition of the studied sample serves as a spectral signature, rather than the level of accumulation of some marker in it. This approach becomes most diagnostically relevant when performing tissue spectral analysis of benign tumors, which accumulate 5-ALA in less than 40% of cases [14], chlorin e6 in less than half of cases [8]. Thus, proposed approach can be used in the diagnosis of nonfluorescent gliomas and other tumors that are difficult to contrast.

Materials and methods

Experimental design

The experimental design is described in detail in one of our previous papers [13]. Studies were performed in the Laboratory of Neurosurgical Anatomy and Preservation of Biological Materials on tumor tissue samples extracted during neurosurgical operations, immediately after removal. Samples from 150 patients with diagnoses of glioblastoma (n = 60), meningioma (n = 38), astrocytoma (n = 19), oligodendroglioma (n = 19), and metastases (n = 14) were examined. From each patient, 1 to 4 biopsy specimens (total 195 tissue samples) were taken with subsequent verification by pathomorphologic examination.

The summarized measurement procedure consisted of the following steps (Fig. 1):

1. registration of endogenous fluorescence spectra of the sample with a 405 nm laser excitation by LESA-01-BIOSPEC spectrometer;
2. registration of spectra of diffuse reflection of white light from the sample and fluorescence spectra of 5-ALA induced protoporphyrin IX in a sample with a 632.8 nm excitation by LESA-01-BIOSPEC spectrometer;
3. registration of the spontaneous spectra of the sample at 785 nm laser excitation with a Raman-HR-TEC-785 spectrometer.

Raman scattering, 5-ALA induced protoporphyrin IX fluorescence, and diffuse reflectance spectra in the 500-600 nm region were measured for all samples. Autofluorescence measurements were performed for 163 samples out of 195.

Since our recent studies on cluster analysis of these data [15] have shown that without partitioning by diagnosis into separate clusters it is possible to separate tumors of meningeal and glial nature, but not different gliomas, all glial tumors were combined into one class in this paper. Fig. 2 shows the scheme of feature vector formation based on the analysis of diffuse reflectance, fluorescence and Raman spectra.

Machine learning methods for processing and analyzing spectral data

Biomedical data often have omissions because some procedures may not have been performed on individual patients due to individual differences or chance circumstances. Other scenarios for the occurrence of these omissions are also possible. Thus, in our case, the feature vector was initially generated from Raman spectroscopy, white light diffuse reflectance and fluorescence spectroscopy data under excitation at 632.8 nm. However, since in this study we were more interested in tumors that did not show contrast by accumulation of 5-ALA induced protoporphyrin IX, since it is these

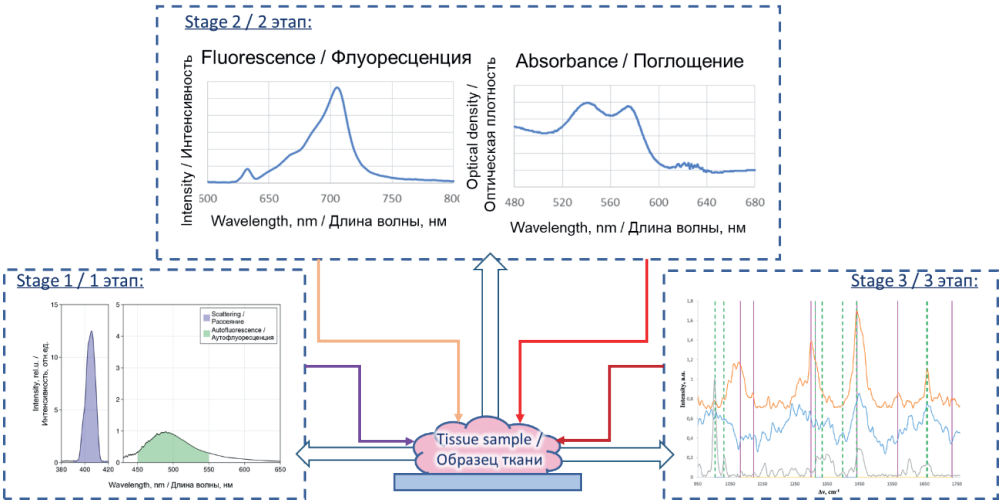

Рис. 1. Схема регистрации спектров флуоресценции, диффузного отражения и комбинационного рассеяния.
Fig. 1. Scheme for registering fluorescence, diffuse reflectance and Raman spectra.

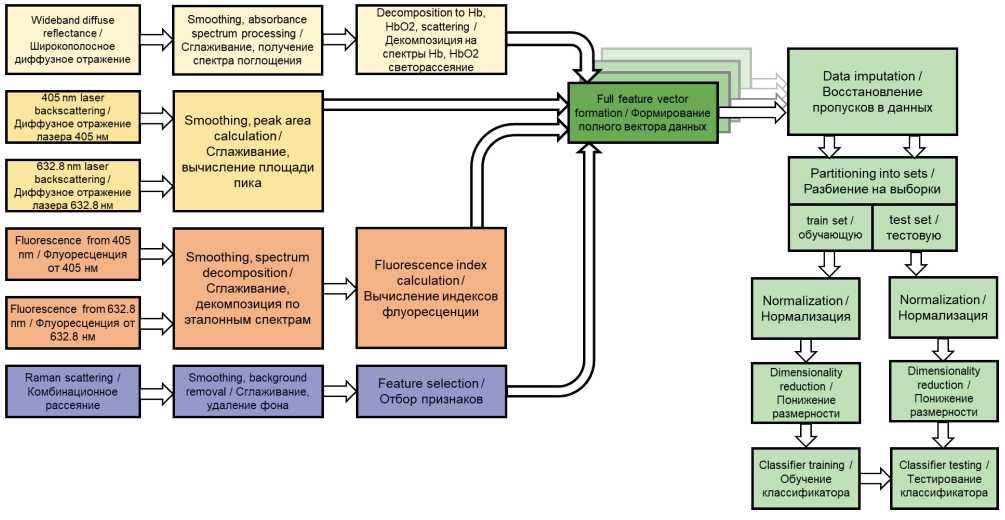

Рис. 2. Схема регистрации спектров, формирования вектора признаков и обучения классификатора.
Fig. 2. Scheme for spectra registration, feature vector generation and classifier training.

tumors that require additional features to differentiate them from healthy tissues, we included the method of recording autofluorescence under 405 nm excitation. Thus, some of the measurements we have do not contain the full range of features. To ensure that all samples can be used for classification, in such cases, the missing features are recovered using information about their values in those samples that have them. There are several approaches to data recovery. One type of interpolation algorithm is univariate interpolation, which interpolates the values in the *i*-th feature dimension using only the non-missing values in that feature dimension. One of the simplest examples of this approach is filling in missing values with the sample mean of that attribute. This approach does not improve for these vectors the quality of classification on this feature, but does not degrade it either, while still allowing these samples to be used in the analysis. In contrast, multivariate missing data interpolation algorithms use the entire set of available features to estimate missing values. This is done by modeling each feature with missing values as a function of other features and using this estimate for imputing values. Cluster analysis can also be used to recover missing data. In the present work, we have used the k-Nearest Neighbors imputer. Each missing feature is reconstructed using values from n nearest neighbors that have a value for that feature. Neighbor feature values are averaged uniformly or weighted by the distance to each neighbor. If more than one feature is missing from a sample, the neighbors for that sample may be different depending on the specific feature being recovered. If the number of available neighbors is less than n and the distances to the training set are not defined, the average value of the training set for a given feature is used in the imputation. If there is at least one neighbor with a certain distance, the weighted or unweighted average of the remaining neighbors will be used in the calculation. If a feature is persistently absent from the training, it is removed during the transformation.

Since we analyze data obtained by different optical-spectral methods, they require unification and selection of significant features in the feature vector. To this end, we performed a two-step dimensionality reduction procedure [16]. Feature filtering removes features (wavelengths, wave numbers, peak positions) that may contain noise or information that lowers the contrast between the studied groups. This procedure reduces the dimensionality of the data and focuses on useful information. The second approach to dimensionality reduction is to project features onto the new space and discard less relevant features. We have demonstrated that a feature pre-filtering step before applying feature projection techniques for dimensionality reduction significantly improves classification results. Dimensionality reduction methods due to feature projection can be categorized into linear and nonlinear methods. Linear methods include principal component analysis (PCA) and linear discriminant analysis (LDA). Among the nonlinear ones we used in this paper are: spectral embedding (Laplacian Eigenmaps, SE), t-distributed stochastic neighbor embedding (t-SNE).

Among the methods used in this paper to classify the labeled data, support vector machine, logistic regression and Bayesian approach with the assumption of independence of features in the vector, referred to as naive Bayes, were used.

The support vector machine amounts to finding the hyperplane boundary between classes, that is one dimension lower than the number of features. In general, two groups of objects in the plane can be separated by a straight line. However, if the boundary between them has a complex shape, we can artificially increase the dimensionality by introducing an additional axis obtained as a function of one of the features, and in the new space find a more appropriate separator between classes. This feature is called the kernel function and its choice can significantly change the classification results. Logistic regression is also based on dividing the data in the feature space into groups using some threshold. In linear regression terms, the class of data is the dependent variable. The probability of falling into each class is described by a sigmoid function with a threshold for classification. A naive Bayesian classifier is based on the application of Bayes' theorem (which allows us to refine the conditional probability of an event, e.g., whether an object belongs to a class based on both a priori probability and new data) with strict (naive) assumptions about feature independence.

Results and discussion

Figs. 3, 4 show the variants of defining tumors by their type – each illustration shows all the results of different classifiers for one of the dimensionality reduction methods. A training sample (50% in each class) was used to train the classifier, and the sensitivity and specificity of the classifier were evaluated on the remaining data.

The results show high specificity in detecting meningiomas (i.e., non-meningiomas falling into non-meningioma classes), but the maximum sensitivity of their detection does not exceed 50% when combining linear discriminant analysis as a dimensionality reduction method and a naive Bayesian classifier.

For distinguishing between normal tissue, tumor tissue, and necrosis, 50% of the samples in each class were used as a training set. For glial tumors, the sensitivity varied between 81% and 94%, with the combination of linear discriminant analysis as a dimensionality reduction method and naïve Bayesian classifier showing the best results (Fig. 5, Table 1). Due to low number of samples

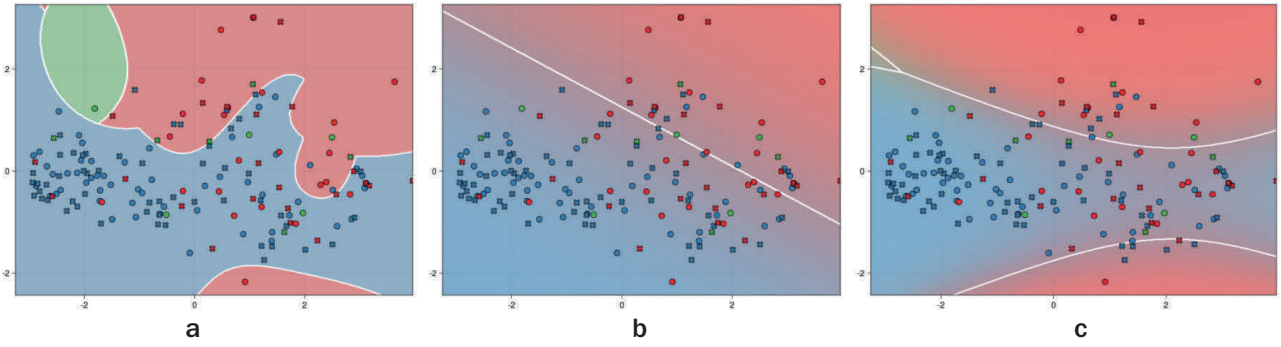

Рис. 3. Классификация образцов по диагнозам (красный – менингиомы, синий – глиомы, зеленый – метастазы) после применения PCA: a – метод опорных векторов; b – логистическая регрессия; c – наивный байесовский классификатор.
Fig. 3. Classification of samples by diagnosis (red – meningiomas, blue – gliomas, green – metastases) after PCA: a – support vector machine; b – logistic regression; c – naive Bayesian classifier.

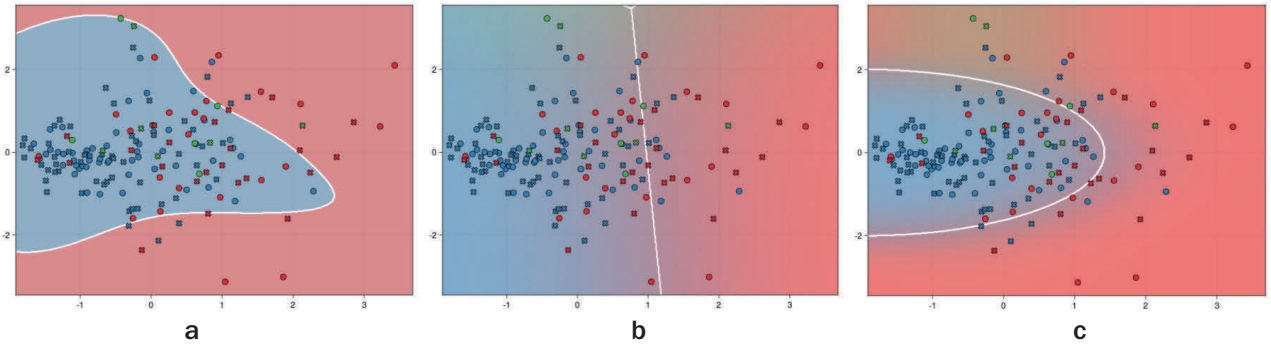

Рис. 4. Классификация образцов по диагнозам (красный – менингиомы, синий – глиомы, зеленый – метастазы) после применения LDA: a – метод опорных векторов; b – логистическая регрессия; c – наивный байесовский классификатор.
Fig. 4. Classification of samples by diagnosis (red – meningiomas, blue – gliomas, green – metastases) after LDA: a – support vector machine; b – logistic regression; c – naive Bayesian classifier.

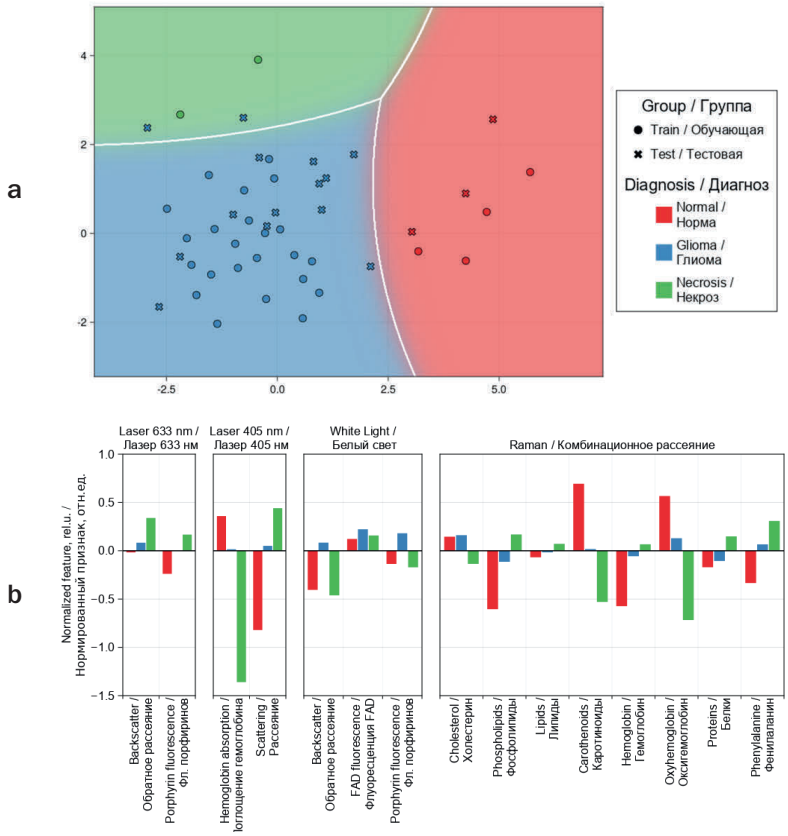

Рис. 5. a – Результаты классификации типов ткани глиом с использованием метода LDA и наивного Байеса, b – Средние нормированные значения признаков в классах в логарифмической шкале.
Fig. 5. a – Results of tissue type classification of gliomas using LDA and naïve Bayes, b – Mean normalized features in classes in logarithm.

Таблица 1
Результаты классификации глиом с использованием LDA и наивного Байеса
Table 1
Results of glioma classification using LDA and naive Bayes

Диагноз Diagnosis	Чувствительность Sensitivity	Специфичность Specificity	Точность Accuracy
Мозговая ткань Brain tissue	100.00%	93.75%	94.74%
Опухоль Tumor	81.25%	100.00%	84.21%
Некроз Necrosis	–	89.47%	89.47%

with necrosis, the sensitivity of detecting necrotic tissue couldn't be assessed.

If we analyze the biochemical components (represented in the logarithm in Fig. 5 b) most pronounced in the classes obtained for gliomas, we see among the characteristics determined by Raman spectroscopy that norma corresponds to a higher content of carotenoids, which are part of the antioxidant defense in healthy brains, and oxygenated hemoglobin with a much lower value of total hemoglobin, while we observe the opposite trends for tumor tissues. For necrosis, we see a significant excess of phenylalanine over other classes, which is practically absent in normal tissue.

Conclusion

This study proposes an approach to the construction of a decision support system based on the formation of a vector of tissue sample features from diffuse reflectance, fluorescence and Raman spectroscopy data. Successive application of dimensionality reduction methods to select the most significant features, recovery of missing data, and automatic classification methods such as support vector machine, logistic regression, and naive Bayes (based on the assumption of feature independence) provided glioma detection with a sensitivity of 94.55% using linear discriminant analysis and logistic regression, but specificity was below 50%. Using a naive Bayesian classifier, however, showed an increase in sensitivity to 81%. As a further line of research, it seems necessary to provide more detailed partitioning of baseline data by tissue type within each diagnosis according to pathomorphologic findings.

Summarizing the results of the work on the search for an alternative and/or burst fluorescence method of tumor tissue differentiation:

1) For non-fluorescent tumors, the most significant indicators are the intensity of elastic light scattering (optical density of tissues decreases due to destructuring of healthy nervous tissue), carotenoid content (decreases in tumors), and changes in the ratio of lipid and protein content.

2) Analysis of the results of classification by biochemical components allowed us to single out phospholipids, carotenoids, phenylalanine, hemoglobin (total and oxygenated) as the most expressed.

3) A classifier on the labeled data can distinguish between normal and glioma tissues with a sensitivity of 81.25% and 100% specificity.

This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-15-2021-1343 dated October 4, 2021).

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POSSIBILITIES OF FLUORESCENCE DIAGNOSTICS IN DETECTING MULTICENTRIC FOCIES OF CERVICAL DYSPLASIA

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Abstract

Colposcopy allows the examiner to localize potential lesions, assess the severity of the lesion, and obtain a colposcopic guided biopsy. This method has limited sensitivity and specificity, raising serious concerns about the possibility of missing cervical dysplasia. Fluorescent methods for diagnosing precancerous diseases of the cervix and early forms of cancer have an extremely high sensitivity, reaching 90%. The presented results of the study allow us to fully declare the high information content of fluorescent colposcopy in identifying dysplastic lesions on the cervix.

Keywords: cervical dysplasia, fluorescent diagnostics, cervical biopsy, photodynamic therapy.

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For citation: Smailova S.B., Shanazarov N.A., Grishacheva T.G., Salmagambetova S.Zh., Aldabergen G.S. Possibilities of fluorescence diagnostics in detecting multicentric focies of cervical dysplasia, *Biomedical Photonics*, 2023, vol. 12, no. 3, pp. 11–14. doi: 10.24931/2413–9432–2023–12-3-11–14.

ВОЗМОЖНОСТИ ФЛЮОРЕСЦЕНТНОЙ ДИАГНОСТИКИ В ВЫЯВЛЕНИИ МУЛЬТЦЕНТРИЧНЫХ ОЧАГОВ ДИСПЛАЗИИ ШЕЙКИ МАТКИ

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Резюме

Кольпоскопия позволяет исследователю локализовать потенциальные поражения, оценить тяжесть поражения и получить кольпоскопически направленную биопсию. Данный метод имеет ограниченную чувствительность и специфичность, вызывая серьезные опасения по поводу вероятности пропуска дисплазии шейки матки. Флуоресцентные методы диагностики предраковых заболеваний шейки матки и ранних форм рака обладают крайне высокой чувствительностью, достигающей 90%. Представленные результаты исследования позволяют в полной мере заявить о высокой информативности флуоресцентной кольпоскопии в выявлении диспластических очагов на шейке матки.

Ключевые слова: дисплазия шейки матки, флуоресцентная диагностика, биопсия шейки матки, фотодинамическая терапия.

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Ссылка для цитирования: Смаилова С.Б., Шаназаров Н.А., Гришачева Т.Г., Сальмагамбетова С.Ж., Алдаберген Г.С. Возможности флюоресцентной диагностики в выявлении мультцентричных очагов дисплазии шейки матки // Biomedical Photonics. – 2023. – Т. 12, № 3. – С. 11–14. doi: 10.24931/2413–9432–2023–12–3-11–14.

Introduction

In 2020, 604127 cases of cervical cancer (CC) and 341831 deaths due to this malignant neoplasm were reported worldwide [1]. CC is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide [2]. In the Russian Federation in 2021, more than 15 thousand women were diagnosed with this pathology for the first time. Mortality from cervical cancer amounted to more than 6 thousand cases [3].

Screening for precancerous diseases and cervical cancer in target groups of patients in the Republic of Kazakhstan (RK) is carried out using routine cytological examination of the Papanicolaou smear. If an abnormal result is detected, by an algorithm, colposcopy and testing to detect DNA of highly oncogenic types of human papillomavirus (HPV) is performed.

Women aged 30 to 70 years are subject to mandatory cancer screening in the Republic of Kazakhstan once every 4 years. According to the results of the cytological screening method for CC, in 2021, a total of 757454 women aged 30–70 years were examined. Of this number, precancerous diseases were identified in 0.99% (7498), and CC was detected in 0.04% (319). The incidence of cervical cancer (the proportion of newly diagnosed cases) was 1804 women (18.3 per 100 thousand female population versus 17.2 in 2020). The mortality rate from cervical cancer in 2021 has not changed compared to 2020 and amounted to 6.0 per 100 thousand female population [4].

Despite the current existence of clear provisions on precancerous processes and CC, the availability of reliable test control (cytological, colposcopic) of CC remains an urgent problem in gynecological oncology to this day [5].

CC is a visually accessible form of a malignant tumor, so the possibilities for early detection are practically unlimited. For this, timely and correct use of accessible and informative diagnostic methods is sufficient. In addition, timely treatment of precancerous processes of the cervix can prevent the development of cervical cancer [6].

It has been proven that the cause of the development of cervical cancer may be persistent HPV infection in the cervical tissue. Human papillomavirus (HPV) is the most common sexually transmitted infection [7]. With long-term persistence of HPV infection in a woman's body, dysplastic processes occur on the cervix, in the absence of treatment of which the next stage of development will be cervical cancer.

The Pap smear is a screening test, and depending on the abnormality, the next step in evaluating the process is a colposcopy. The procedure involves treating the cervix with a 5% acetic acid solution, followed by examining the integumentary epithelium under magnification. Pathologically altered areas of the cervical mucosa are characterized by persistent whitening of the epithelium. A targeted biopsy taken from these areas is sent for histological examination to determine the nature of the changes. Colposcopy, which is currently included in World Health Organization (WHO) guidelines for women infected with HPV, remains the reference standard for biopsy to confirm precancer and CC [8].

One of the priority areas in modern medicine is the use of fluorescence diagnostics (FD) through the introduction of exogenous photosensitizers (PS). When they enter the bloodstream, PSs most often bind to serum proteins, forming complex compounds [9]. The resulting complexes of PS with proteins are absorbed by endothelial cells in the capillaries of the bloodstream. Then they bind to the adventitia of blood vessels and PS enters the extracellular matrix with subsequent accumulation and retention in pathologically altered cells. When excited by blue light, red fluorescence is generated, resulting in a distinct fluorescent contrast between tumor/pretumor and healthy surrounding tissue [10].

The use of PD methods in the complex diagnosis of precancerous changes in the cervix increases diagnostic efficiency in identifying the location and size of lesions, thus facilitating more complete visualization for subsequent treatment. The main parameter of the reliability of this diagnostic method is histological confirmation of the dysplastic status of fluorescent lesions. At the same time there is a correlation between the degree of tissue dysplasia and fluorescence intensity. Fluorescence imaging can facilitate the detection of extraclinical lesions [11].

Fluorescence diagnosis represents a promising opportunity in the diagnosis of diseases in a wide range of medical disciplines, such as gynecology, dermatology, gastroenterology, surgery, neurosurgery and urology. In gynecology, many studies have been conducted evaluating the utility of fluorescent detection of cervical dysplasia, breast cancer, endometrial diseases, ovarian cancer and endometriosis [12].

A number of studies show that, due to high selectivity for tumors and low toxicity to healthy tissues, diagnostics based on modern PSs are a promising tool for the non-invasive identification of cervical intraepithelial neoplasia [13]. The use of fluorescent colposcopy allows the doctor to adequately assess the size and boundaries of lesions to select PDT parameters [14]. In the present study, we assessed the informativeness of fluorescent colposcopy in identifying cervical dysplasia by histological examination of biopsy specimens from foci of red fluorescence.

Materials and Methods

The study was performed as part of the project for the implementation of the scientific and technical program BR18574160 "Development of innovative technologies that increase the efficiency of diagnosis and treatment

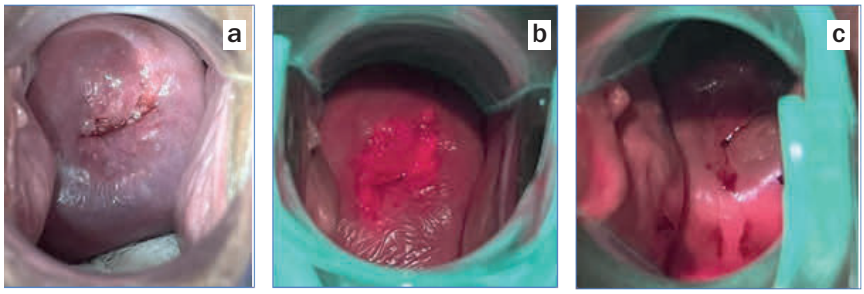

Рис. 1. Кольпоскопическая картина шейки матки пациентки с HSIL и 4 типами ВПЧ: a – в видимом свете после обработки шейки матки 5% раствором уксусной кислотой; b,c – в режиме флуоресцентного обследования.
Fig. 1. Colposcopic image of the cervix of a patient with HSIL and 4 types of HPV: a – in visible light after treating the cervix with a 5% solution of acetic acid; b,c – in fluorescent examination mode.

of background and precancerous diseases of the cervix associated with the human papillomavirus", agreement No. 39-PTsF-23-24 dated January 25, 2023, carried out at the Medical Hospital Center for Administration of Presidential Affairs of the Republic of Kazakhstan, aged 18 to 49 years. The average age was 37.3±4.9 years. A positive result for highly oncogenic types of PCR for HPV and an established cytological diagnosis distributed as follows: LSIL n=38 (95%) and HSIL n=2 (5%), 7 (17.5%) women had previously undergone surgical treatment of the cervix.

The colposcopic examination was performed on a modern device – video colposcope SLV-101 HD with a digital FullHD video camera, with LED lighting, optical zoom up to 23 times and recording of images on a personal computer with an installed program, with a built-in yellow filter for leveling ultraviolet light. A chlorine-type drug was used as a photosensitizer.

Among 40 participants, highly oncogenic HPV types were distributed as follows: type 16 – in 12 (24.5%) patients, type 31 – in 7 (14.3%) patients, type 58 – in 7 (14.3%) patients, type 18 – in 5 (10.2%) patients, type 33 – in 3 (6%) patients, type 35 – in 3 (6%) patients, type 45 – in 3 (6%) patients, type 56 – in 3 (6%) patients, type 59 – in 3 (6%) patients, type 52 – in 2 (4.1%) patients, type 51 – in 1 (2%) patients.

Visual observation of the fluorescence images was possible with the naked eye. For documentation, the video colposcope camera was equipped with additional functions: a yellow filter was built into the eyepiece to improve fluorescence detection and neutralize the violet light of an ultraviolet flashlight. This allowed better targeting of negative fluorescence regions and a clear delineation of positive fluorescence images compared to negative regions by increasing the contrast between red and blue light.

Results

As a result of the study, the following data were obtained: out of 40 patients, fluorescent lesions were histologically verified as dysplasia in 39 (97.5%) women. In one case, fluorescence colposcopy revealed a combined pathology of the genital tract in the patient in the form of morphologically confirmed moderate dysplasia of the vaginal mucosa (the woman was removed from the project for further examination).

The high percentage of recurrence of cervical dysplasia after surgery, in the study in 17.5% of participants, can be explained by underestimation of the prevalence of the process and, as a consequence, non-radical treatment.

Clinical observation

A 34-year-old patient with HSIL and 4 types of HPV underwent colposcopy of the cervix in visible light and fluorescence diagnosis. In Fig. 1a a colposcopic picture after treatment of the cervix with a 5% solution of acetic acid can be seen, where a rough mosaic, open glands with a rough rim of keratinization are clearly visible. At fluorescence colposcopy (Fig. 1 b, c), areas of red fluorescence correspond to areas of aceto-white epithelium, and a bright glow is additionally detected in the posterior fornix and the right lateral wall of the vagina. A biopsy was taken from this area. The histological result is moderate epithelial dysplasia of the vaginal epithelium (VAIN 2). This pathology is usually combined with cervical dysplasia, while it is rare as an independent nosology,.

Conclusion

Fluorescence colposcopy makes it possible to diagnose multifocal lesions on the cervix, in particular pathologies localized outside the cervix, and to correctly assess the boundaries of the lesion, not inferior to colposcopy using the acetic acid test.

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PHOTO AND SPECTRAL FLUORESCENCE ANALYSIS OF THE SPINAL CORD INJURY AREA IN ANIMAL MODELS

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Abstract

The purpose of the work is to follow the dynamics of changes in fluorescent signals in the near-surface layers of tissue of injured areas of the back of laboratory animals, which will allow, by indirect evidence, to evaluate the information content of fluorescence diagnosis for subsequent possible diagnostic monitoring of photodynamic therapy of the spinal cord. The model animals were Wistar rats. Two types of contusions were modeled: pneumocontusion and contusion by a falling load. Methylene blue and indocyanine green were used as photosensitizers. Fluorescence measurements were carried out by imaging and spectrometric methods. A stroboscopic fluorescence imager with an excitation wavelength of 630 nm was used to acquire fluorescence images. The LESA-01-BIOSPEC spectrometer with a He-Ne laser excitation allowed to obtain spectra. It was shown that both methods make it possible to estimate the fluorescence value of methylene blue and indocyanine green in the tissues under study. Moreover, the photographic method also allows to obtain the spatial distribution of fluorescence. The general trend found in the data is a more intense and uniform fluorescence of the dorsal region of rats with methylene blue and a less intense, but more contrasting distribution of indocyanine green. The presented methods are non-invasive, which makes them attractive for diagnostic use. However, due to the shallow depth of signal reception, the condition of the spine can be determined only indirectly, by the condition of the near-surface layers of tissue that accumulate the photosensitizer.

Key words: Fluorescence diagnosis, spectral analysis, methylene blue, indocyanine green, paravertebral area, spinal trauma.

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For citations: Udeneev A.M., Kalyagina N.A., Reps V.F., Kozlova V.V., Pigunova L.A., Pozdnyakov D.I., Skobeltsin A.S., Loschenov V.B. Photo and spectral fluorescence analysis of the spinal cord injury area in animal models, *Biomedical Photonics*, 2023, vol. 12, no. 3, pp.16-20. doi: 10.24931/2413–9432–2023–12-3-16-20.

ФОТО И СПЕКТРАЛЬНЫЙ ФЛУОРЕСЦЕНТНЫЙ АНАЛИЗ ОБЛАСТИ ТРАВМЫ СПИННОГО МОЗГА НА ЖИВОТНЫХ МОДЕЛЯХ

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Резюме

Цель работы – проследить динамику изменения флуоресцентных сигналов в приповерхностных слоях тканей травмированных участков спины лабораторных животных, что позволит, по косвенным признакам, оценить информативность флуоресцентной диагностики для последующего возможного диагностического мониторинга фотодинамической терапии спинного мозга. Модельными животными были крысы Вистар. Моделировалось два типа контузий: пневмоконтузия и контузия падающим грузом. Флуоресцентные измерения проводились фотографическим и спектрометрическим методом с препаратами метиленовый синий и индоцианин зеленый. Для фоторегистрации флуоресцентного ответа использовался стробоскопический флуоресцентный имиджер с длиной волны возбуждения 630 нм. Спектральные измерения проводились с помощью спектрометра ЛЕСА-01-БИОСПЕК, с возбуждением He-Ne лазером (632,8 нм). Показано, что оба метода позволяют оценивать величину флуоресценции метиленового синего и индоцианина зелёного в исследуемых тканях, а фотографический метод позволяет также получить пространственное распределение флуоресценции. Общая тенденция, обнаруженная в полученных данных – более интенсивная и равномерная флуоресценции дорсальной области крыс метиленовым синим, и менее интенсивное, но более контрастное распределение индоцианина зелёного. Представленные методы неинвазивны, что делает их привлекательными для диагностического использования. Однако из-за малой глубины приема сигнала состояние позвоночника можно определить лишь косвенно, по состоянию приповерхностных слоев тканей, накапливающих фотосенсибилизатор.

Ключевые слова: Флуоресцентная диагностика, спектральный анализ, метиленовый синий, индоцианин зелёный, область спинного мозга, спинальная травма.

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Ссылка для цитирования: Уденеев А.М., Калягина Н.А., Репс В.Ф., Козлова В.В., Пигунова Л.А., Поздняков Д.И., Скобельцин А.С., Лощенов В.Б. Фото и спектральный флуоресцентный анализ области травмы спинного мозга на животных моделях // Biomedical Photonics. – 2023. – Т. 12, № 3. – С. 16-20. doi: 10.24931/2413–9432–2023–12–3-16-20.

Introduction

Despite the significant efforts of clinicians around the world, spinal cord injury (SCI) remains one of the most pressing problems in modern neurosurgery. Thus, the social and economic consequences of this medical problem cannot be overstated [1]. Healthcare studies in developed countries indicate an incidence of SCI of 4–6 cases per 100,000 inhabitants per year, with severe long-term consequences for patients and, as a result, a huge impact on society.

Fluorescence diagnosis is based on the excitation of fluorescence of a photosensitizer accumulated in biological tissues and registration of the fluorescent signal from the tissue under study, followed by analysis. Classically, this procedure is used to identify foci of neoplasms of various localizations and their boundaries [2, 3]. In addition, the method is often used intraoperatively for navigation during surgery [4, 5]. Moreover, fluorescence diagnosis can be used, for example, to assess the effectiveness of photodynamic therapy (PDT) (measurements before/during/after a PDT session) [6, 7]. This possibility is considered in this work to analyze the prospects of fluorescence diagnosis when performing PDT for spinal cord injuries. Previously, fluorescence studies have already been used for the spinal cord to identify and influence tumor neoplasms [8-10] using various photosensitizers [11], as well as for invasive studies of a different nature [12-14].

The purpose of the present work is to follow the dynamics of changes in fluorescent signals in the near-surface layers of tissue of injured areas of the back of laboratory animals, which will allow, by indirect evidence, to evaluate the information content of fluorescence diagnosis for subsequent possible diagnostic monitoring of PDT of the spinal cord.

Materials and Methods

Model animals

The experimental animals were Wistar rats, 2.5-3 months old, females weighing 150–200 g, and males weighing up to 240 g. Modeling of contusion injury was carried out in 2 modifications – pneumo contusion and moderate contusion by a falling weight. Pneumo contusion was simulated by a blank shot at point-blank range from an IZH-53M spring pneumatic pistol. When modeling a moderate contusive spinal cord injury, a custom-made setup was used. The setup was in the form of a pipe 50 cm high and 20 mm in diameter, mounted on a tripod, dropping a cylindrical load weighing 350 g from a height of 50 cm, which is equivalent to 1.96 N/cm^2 in terms of force on the vertebrae. The animal's behavior was recorded using a Samsung A9 smartphone camera. Animals were removed from the experiment by immediate decapitation under chloral hydrate anesthesia. Imaging and spectral measurements of fluorescence were carried out once a day for 4 days, starting from the day of the simulated injury (1 hour after injury).

Photosensitizers

Fluorescence diagnosis was carried out using two photosensitizers – methylene blue (MB) and indocyanine green (ICG). Drug administration regimens are presented in Table 1.

Таблица 1
Режим введения фотосенсибилизаторов
Table 1
Modes of administration of photosensitizers

Фотосенсибилизатор Photosensitizer	Способ введения Administration way	Доза Dose	Экспозиция, мин. Exposition, min	Режимы введения Administration regimens
МС MB	внутрибрюшинно intraperitoneally	20 мг/кг 20 mg/kg	10	Раз в день, перед флуоресцентной диагностикой, в течение 4 дней once a day before FD for 4 days
ИЗ ICG	внутрибрюшинно intraperitoneally	10 мг/кг 10 mg/kg	5	Раз в день, перед флуоресцентной диагностикой, в течение 4 дней once a day before FD for 4 days

МС – метиленовый синий, ИЗ– индоцианиновый зеленый.
MB – methylene blue, ICG – indocyanine green.

For a better understanding of the working ranges of the technique under study, see the emission spectra of the photosensitizers used in the work [15] and the fluorescence spectra of endogenous fluorophores [16, 17].

Equipment

For photographic registration of the fluorescence response of photosensitizers and endogenous fluorophores, a stroboscopic fluorescence imager (SFI) was used. The SFI consisted of a red LED with a central wavelength of 630 nm and an optical power of 1 W to excite the fluorescence of light-sensitive components accumulated in biological tissues, two white LEDs (with an optical power of 200 mW each) to create uniform illumination of the surgical field, as well as one violet LED (not used in this study) (Fig 1a). The spectrum of the red LED was corrected by a bandpass filter with a central wavelength of 636 nm. A long pass filter (LPF) with a cut-on frequency of 660 nm was installed in front of the camera lens. SFI allowed to obtain pairs of frames: one frame with the fluorescence excitation LEDs and backlight LEDs turned on (respectively, with fluorescence) and the other with only backlight LEDs turned on (background frame). Subtracting the background frame helped to reduce the impact of background light.

Fluorescence index

The fluorescence index (FI) was used to quantify fluorescence intensity when processing spectral data. It was calculated by dividing the area under the fluorescence spectrum curve by the area under the scattering spectrum curve of the excitation He-Ne laser.

Results

To distinguish the spectra of photosensitizers from the spectrum of endogenous fluorophores in Fig. 2 a spectrum taken on an intact animal is shown.

Fluorescence images

Below are examples of fluorescence images obtained in the area of spinal cord injury in laboratory animals obtained with SFI (Fig. 3).

Spectra

Below are the examples of obtained spectra from the region of spinal cord injury in laboratory animals, obtained using a spectrometer for the methylene blue (MB) (Fig. 4) and indocyanine green (ICG) (Fig. 5).

Fig. 4a shows spectra and diagrams of fluorescence signals obtained in an area away from the injury (healthy area). Fig. 4b shows spectra and diagrams of

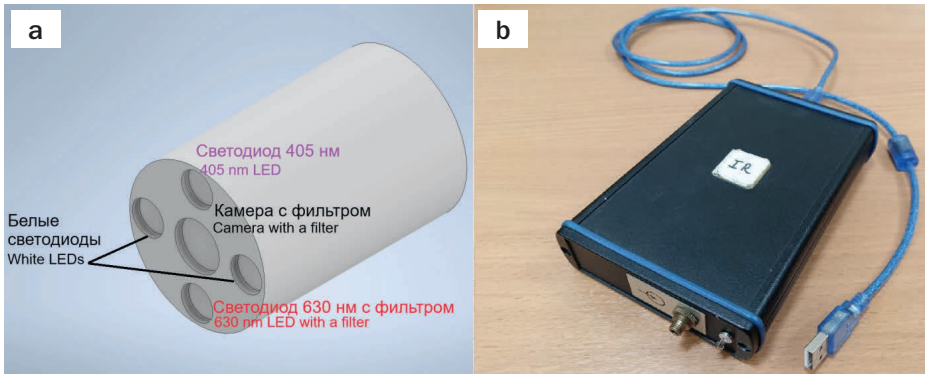

Рис. 1. Диагностическое оборудование: a – стробоскопический флуоресцентный имиджер (СФИ); b – спектрометр ЛЕСА-01 БИОСПЕК.
Fig. 1. Diagnostic equipment: a – stroboscopic fluorescence imager (SFI); b – spectrometer LESA-01 BIOSPEC.

fluorescence signals taken in the area of injury (trauma area). Histograms express fluorescence indices (FI) (see description in the "Materials and Methods" section) for the corresponding rat on different days in chronological order (day 1 – day 4) and characterize the accumulation of the photosensitizer in the study area. The histogram columns correspond in color to the presented spectra.

The "norm" was considered to be the area of the back located at a distance from the area of the animal's injury. The "trauma" was considered to be the directly injured area of the back.

The distinctive fluorescence peak of indocyanine green was recorded around 880 nm (Fig. 5). In some spectra, this peak was nearly indistinguishable from the tissue autofluorescence spectral signal, which did not allow reliable analysis.

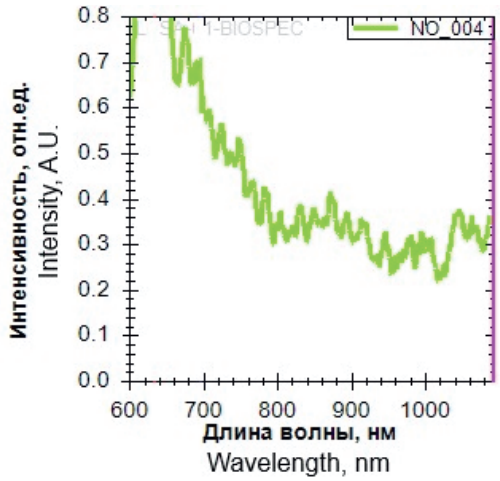

Рис. 2. Спектр флуоресценции спинной области интактного животного.
Fig. 2. Fluorescence spectrum of an intact animal dorsal area.

Discussion

The study showed that both methods under consideration can reliably detect the fluorescence signal from methylene blue, both in the area of injury and in normal conditions. The general trend, noticeable both in the spectra and in the images, is a more intense (in the case of spectra) and brighter and uniform (in the case of images) fluorescence of the dorsal region of rats with methylene blue than with indocyanine green. The relatively weak signal from indocyanine green is explained by the suboptimal wavelength of the exciting radiation

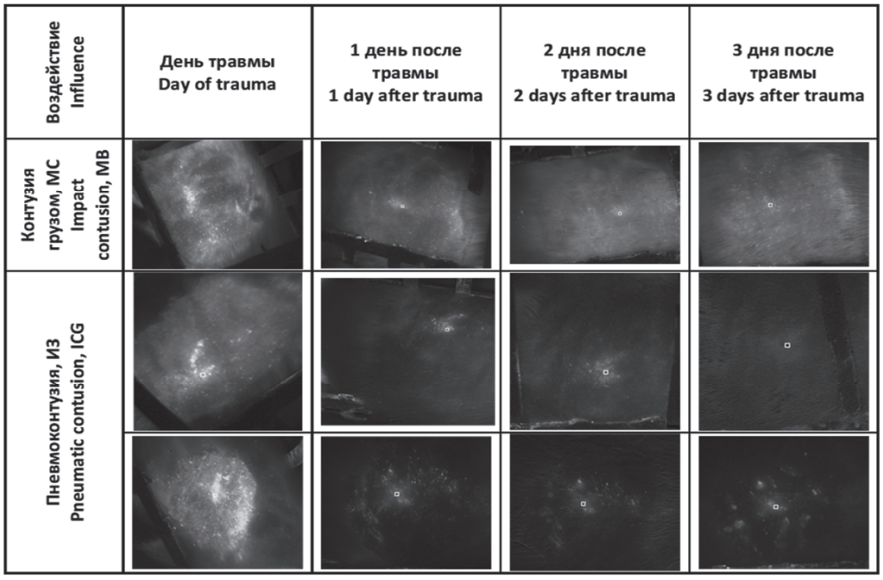

Рис. 3. Примеры СФИ изображений флуоресценции метиленового синего (МБ) и индоцианина зеленого (ИЗ), полученных на лабораторных животных в ходе исследований на 1-4 сутки после моделируемой травмы спинного мозга (включая день травмы).
Fig. 3. Examples of SFI fluorescence images of methylene blue (MB) and indocyanine green (ICG) obtained on laboratory animals during studies on days 1-4 after simulated spinal cord injury (including the day of injury).

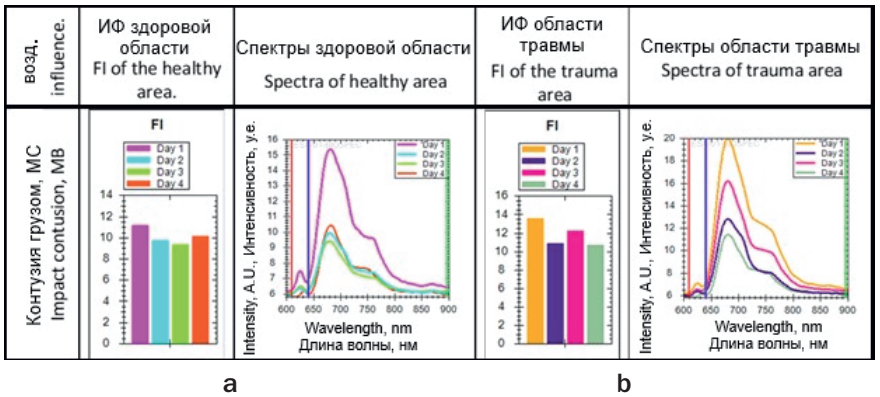

Рис. 4. Примеры спектров флуоресценции метиленового синего (МБ), полученных на лабораторных животных в ходе исследований на 1-4 сутки после моделирования травмы спинного мозга (ИФ – индекс флуофесценции): a – область за пределами травмы; b – зона повреждения спинного мозга.
Fig. 4. Examples of methylene blue (MB) fluorescence spectra obtained on laboratory animals during studies on days 1-4 after modeling spinal cord injury (FI – fluorescence index): a – area outside the injury; b – area of the spinal cord injury.

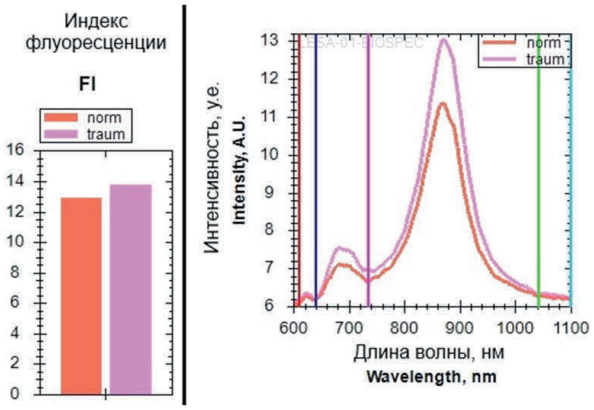

Рис. 5. Примеры индексов флуоресценции и спектров флуоресценции индоцианина зеленого (ИЗ), полученных в области нормы и травмы.
Fig. 5. Examples of indocyanine green (ICG) fluorescence indexes and fluorescence spectra obtained from normal area and the area of trauma.

(636 nm at SFI and 632.8 at spectral measurements), which in the wavelength range is located closer to the absorption band of methylene blue. However, it is worth noting that in the case of indocyanine green, a more contrasting fluorescence pattern is observed in the images. This stronger contrast in measurements can be explained by its accumulation in the main vessels and lymph flows.

Analysis of the averaged data results shows that on the first day of measurements (immediately after injury) the strongest MB and ICG fluorescence signal is visible in the injured area, which is explained by the fact that the increase in edema and the formation of hematomas occur gradually, therefore, there were fewer obstacles to detecting the signal in the injured area than in the following days. In subsequent days, the intensity of the fluorescence signal in the area of injury decreases. In the normal area, the signal decreases more slowly and almost imperceptibly, and the fluorescence intensity is lower than in the injured area. The results obtained in the form of images show a similar picture: the injury attenuation function is ahead of the normal attenuation function, due to which the contrast of the injury against the normal background in frames obtained with SFI is reduced.

Also, intense fluorescence of both drugs was observed both in hematomas and in areas of skin damage after shaving, which may be caused by the accumulation of the drug circulating in the bloodstream in hyperemia. Therefore, in future experiments, the rats should be depilated instead of shaving to avoid adding damage to the skin and thus introducing uncertainty into the experiment.

Conclusion

The presented methods are non-invasive, which makes them attractive and promising for diagnostic use. However, due to the shallow depth of signal reception, the condition of the injured spine can be determined only indirectly, by the fluorescence signals from the near-surface layers of the back accumulating photosensitizers. However, detecting the difference in the fluorescence signals from the "normal" area and the area of injury, as well as in the dynamics of the signal by day, makes it possible to detect and evaluate the degree of hematoma healing and reduction of hyperemia, which are often indistinguishable to the naked eye. This suggests that the method can be potentially used to control PDT in spinal cord injuries.

Acknowledgements

This work was carried out as part of a state assignment "Development of technology for immunotherapeutic treatment of spinal cord injuries" Registration number: 122041300077-1.

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CLINICAL CASE OF SUCCESSFUL APPLICATION OF PHOTODYNAMIC THERAPY IN ADVANCED VULVAR CANCER

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Abstract

A significant therapeutic effect of photodynamic therapy (PDT) is shown in a patient with extensive vulvar cancer after ineffective surgical and chemoradiotherapy. During the year, three courses of local PDT with a photosensitizer based on chlorin e6 were carried out. The photosensitizer was administered intravenously three hours before irradiation at a dose of 1.2 mg/kg. For laser irradiation (662 nm) of the vulvar tumor, a light guide for external irradiation was used: the power density was 0.2 W/cm^2, the light dose was from 100 to 250 J/cm^2. As a result of treatment, tumor regression and stable remission are observed. The patient remains under observation.

Key words: vulvar cancer, local photodynamic therapy, clinical case, photolon.

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For citation: Shanazarov N.A., Grishacheva T.G., Aldabergen G.S., Smailova S.B., Salmaganbetova Zh.Zh. Clinical case of successful application of photodynamic therapy in advanced vulvar cancer, *Biomedical Photonics*, 2023, vol. 12, no. 3, pp. 21–24. doi: 10.24931/2413–9432–2023–12-3-21–24.

КЛИНИЧЕСКИЙ СЛУЧАЙ УСПЕШНОГО ПРИМЕНЕНИЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ПРИ РАСПРОСТРАНЕННОМ РАКЕ ВУЛЬВЫ

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Резюме

Показан значимый лечебный эффект фотодинамической терапии (ФДТ) у пациентки с обширным раком вульвы после малоэффективной оперативной, химиолучевой терапии. В течение года проведено 3 курса локальной ФДТ с фотосенсибилизатором на основе хлорина е6. Фотосенсибилизатор вводили внутривенно за 3 ч до проведения облучения в дозе 1,2 мг/кг. Для лазерного облучения (662 нм) опухоли вульвы использовали световод для наружного облучения: плотность мощности составляла 0,2 Вт/см^2, световая доза от 100 до 250 Дж/см^2. В результате лечения наблюдается регрессия опухоли и стойкая ремиссия. Пациентка остается под наблюдением.

Ключевые слова: рак вульвы, локальная фотодинамическая терапия, клинический случай, фотолон.

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Для цитирования: Шаназаров Н.А., Гришачева Т.Г., Алдаберген Г.С., Смаилова С.Б., Сальмаганбетова Ж.Ж. Клинический случай успешного применения фотодинамической терапии при распространенном раке вульвы // Biomedical Photonics. – 2023. – Т. 12, № 3. – С. 21–24. doi: 10.24931/2413–9432–2023–12–3-21–24.

Introduction

Today, the frequency of precancerous diseases of the female external genitalia is one of the most pressing problems of the female population. According to WHO, 46% of premenopausal women worldwide have dystrophic diseases of the vulva, which, against the background of positive HPV, can develop into dysplasia and then into pre-invasive and invasive vulvar cancer [1, 2].

Diagnosis of precancerous diseases of the female external genitalia is based on anamnestic data and examination with a colposcope – vulvoscopy – which allows one to determine the boundaries of pathologically altered tissues [3]. Final confirmation of the diagnosis is possible after cytological and histological conclusions [4]. The reliability of the cytological method in determining the severity of vulvar intraepithelial neoplasia is low due to concomitant severe inflammation, hyperkeratosis and atrophy. Histological examination is performed in the presence of complaints and visually detectable pathological changes [5-7].

The frequency of vulvar cancer in the general structure of gynecological oncological diseases is 4-6% of all cancer cases and is detected in 2-4 women per 100,000 population. About 4 out of 10 women who develop vulvar cancer die. The overall 5-year survival rate for all patients with vulvar cancer is 72% [6].

The main management strategy for patients with vulvar cancer is surgical treatment. [8-11]. Chemoradiotherapy is indicated in unresectable cases of vulvar cancer. Treatment in this case is aimed at slowing the progression of the disease and reducing the tumor mass. In some cases, radiation and chemotherapy may precede surgery, allowing to reduce the tumor size, which creates the background for radical surgery. For the same purpose, it is possible to carry out photodynamic therapy (PDT), which has proven to be an effective method for treating tumor diseases [9, 10].

We present a clinical case of PDT application for advanced vulvar cancer.

Patient G., 65 years old, applied to the PDT Center of the Hospital of the Medical Center of the Presidential Administration of the Republic of Kazakhstan, Astana in September 2022 with complaints of a formation in the vulva and vagina, pain in the vagina, occasional "shooting" pain in the area pubis, and discomfort when walking.

The patient was observed and treated at the place of residence with a diagnosis of malignant neoplasm of the vulva of an unspecified part (TIbN0M0), clinical group 3. Concomitant pathology: insulin-dependent diabetes mellitus, varicose veins of the lower extremities, chronic venous insufficiency class 2.

From the anamnesis it is known that in 2018 vulvectomy was performed; in 2020, due to the instability of the oncological process, a Ducuing operation on the right and left and a radical vulvectomy were performed; in 2021, a locoregional recurrence was detected, and radiation therapy was carried out according to a radical program, using the TERAGAM device in statistical mode with counter-propagating fields on the tumor of the vulva and areas of regional metastasis with a single focal dose of 2 Gy and a total focal dose of 40 Gy.

In 2022, metastatic lesions of the vagina and regional lymph nodes were identified, four courses of palliative chemotherapy (PCT) (ondasetron, paclitaxel, cisplastin) were performed without effect. Since August 2022 there has been an extensive vaginal formation, according to biopsy it is a morphologically squamous cell keratinizing carcinoma, progression.

On vaginal examination revealed that the external genitalia are scarred and atrophic; vagina is short and narrow; in the mirror a dense woody formation with a diameter of 5.0×5.5×4.0 cm is visualized on the left from the edge to the vaginal vault; in the middle there is a purulent ulcer with a dense yellow coating (Fig. 1a). The secretion is serous, with a putrid odor; the cervix is atrophic; the edge of the cervix is tightly covered by the formation, visualization is difficult, and bimanual examination is difficult due to pain and the presence of a volume vaginal formation.

Clinical diagnosis: vulvar cancer T1bN0M0; condition after surgical treatment; recurrence in 2021; condition after external beam radiation therapy (EBRT); condition after 4 courses of chemotherapy; recurrence of vulvar cancer; local chemotherapy in the process.

The patient's treatment tactics were discussed by a multidisciplinary group. Taking into account the localization of the tumor and the lack of response to chemoradiotherapy, a decision was made to perform local PDT.

Upon admission, the patient's condition was satisfactory. The patient signed a voluntary informed consent for PDT.

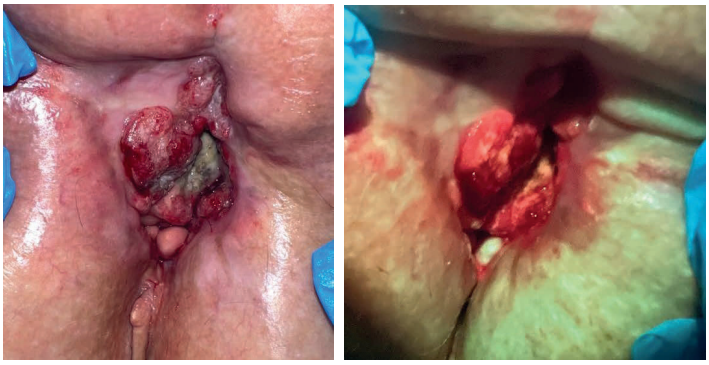
The first course of PDT was conducted on September 5, 2022.

Operation protocol:

Stage 1: intravenous administration of a photosensitizer (PS) based on chlorin e6 (Photolon) at a dose of 1.2 mg/kg. The calculated dose of the drug was dissolved in 200 ml of 0.9% physiological solution and administered over 30 minutes.

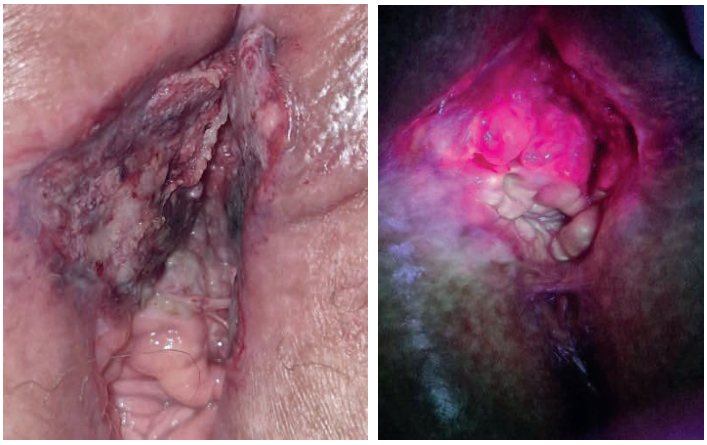
Stage 2: fluorescence diagnostics (FD). Three hours after the end of intravenous administration of PS, FD was performed using a LED illuminator "LED physiotherapy device" (Polironic, Russia) in the wavelength range 400±10 nm. When irradiated in this spectral wavelength range, the accumulation of PS in the tumor was recorded and the boundaries of the pathological focus were determined (Fig. 1b).

Stage 3: PDT. Under local anesthesia, local PDT was performed by irradiating the vagina using a Lakhta Milon laser device (Kvalitek LLC, Russia) at a wavelength of 662



a b

Рис. 1. Рак вульвы T1bN0M0 (состояние после оперативного лечения в 2018 и 2020 г., после ДЛТ и 4 курсов ПХТ без эффекта): a – осмотр в белом свете; b – осмотр в режиме флуоресценции.
Fig. 1. Cancer of the vulva T1bN0M0 (status after surgical treatment in 2018 and 2020, after radiotherapy and 4 courses of chemotherapy without effect): a – examination in white light; b – examination in fluorescence mode.



a b

Рис. 2. Состояние вульвы через 3 мес после 1-го курса ФДТ: a – осмотр в белом свете; b – осмотр в режиме флуоресценции.
Fig. 2. Condition of the vulva 3 months after the 1st course of PDT: a – examination in white light; b – examination in fluorescence mode.

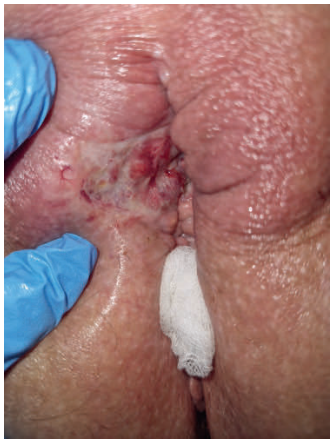


Рис. 3. Состояние вульвы после 3-го курса ФДТ.
Fig. 3. Condition of the vulva after the 3rd course of PDT.

nm in a continuous mode of generation. Irradiation parameters: diameter of the irradiation field – 2.5 cm; power 1.9 W; power density – 0.38 W/cm^2; exposure of one field – 9 min; light dose – 200 J/cm^2; number of fields – 7. The procedure was accompanied by moderate pain. In satisfactory condition, the patient was discharged for ambulatory observation by a gynecological oncologist at the place of residence. The observance of light conditions is recommended to the patient.

In the postoperative period, moderate pain was observed, which required the use of local application of oflomelid ointment and systemic use of non-steroidal anti-inflammatory drugs. Local swelling and hyperemia were noted. After 7-10 days, tumor necrosis formed.

During a follow-up examination one month after the 1st course of PDT, partial destruction of the tumor was noted.

In December 2022, taking into account the partial preservation of the tumor process, it was decided to conduct the second course of PDT. The operation protocol was the same as during the first course. The condition of the vulva and fluorescent glow before PDT are shown in Fig. 2.

In May 2023, the third course of PDT was performed. During a year, it was possible to restrain tumor growth through multi-course treatment. At the moment, the patient's condition is stable. Figure 3 shows the result after the third course of PDT.

Today, in the treatment of precancerous conditions of the female external genitalia, treatment with local PDT plays a significant role [12-17].

In the presented clinical case, local PDT was performed and stabilization of the tumor process was achieved during the treatment. The prognosis for the patient is favorable.

Thus, the use of the PDT method can be used in combination with other methods to increase clinical effectiveness. This determines the relevance of the development of this method in the treatment of oncological and dysplastic diseases of the vulva.

Conclusion

The above clinical case suggests that for patients with the recurrence of the vulvar cancer and ineffectiveness of chemoradiotherapys, PDT allows to achieve a significant regressive effect and stabilize the tumor process.

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PHOTODYNAMIC THERAPY IN NEUROONCOLOGY

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Abstract

Literature review reflects the current status and development status of intraoperative photodynamic therapy in neurooncology and discusses the results of the most important studies on photodynamic therapy (PDT). We searched the Pubmed, EMBASE, Cochrane Library and eLibrary databases for publications published between January 2000 and December 2022. Found 204 publications in foreign sources and 59 publications in domestic editions, dealing with the issues of photodynamic therapy in neurooncology. An analysis of the literature has shown that intraoperative PDT in neurooncology is an important tool that contributes to increasing the radicality of the operation and local control. The basic rationale for the effectiveness of PDT lies in the study of the pathways leading to the complete devitalization of a malignant tumor, the study of the mechanisms of the local and systemic immune response. In addition, subcellular targets in PDT are determined by the properties of photosensitizers (PS). Second generation PSs have already been introduced into clinical practice. The effectiveness of PDT using photoditazine, 5-aminolevulinic acid has been demonstrated. The mechanisms of action and targets of these PS have been established. In Russia, a number of studies have repeatedly shown and proved the clinical effectiveness of PDT in groups of neurooncological patients with glial tumors and secondary metastatic tumors, but so far, the method has not been included in the clinical guidelines for the provision of high-tech neurosurgical care. There is certainly a need for further development of PTD techniques in neurooncology, especially in patients at high risk of recurrence and aggressive CNS tumors.

Key words: photodynamic therapy, photosensitizer, photoditazine, 5-ALA, neurooncology, apoptosis, necrosis, meningioma, recurrence, glioblastoma, metastasis.

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For citation: Olyushin V.E., Kukanov K.K., Nechaeva A.S., Sklyar S.S., Vershinin A.E., Dikonenko M.V., Golikova A.S., Mansurov A.S., Safarov B.I., Rynda A.Y., Papayan G.V. Photodynamic therapy in neurooncology, *Biomedical Photonics*, 2023, vol. 12, no. 3, pp. 25–35. doi: 10.24931/2413–9432–2023–12-3- 25–35.

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В НЕЙРООНКОЛОГИИ

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Резюме

Выполнен обзор литературы, отражающий современное состояние и степень разработанности методики интраоперационной фотодинамической терапии (ФДТ) в нейроонкологи. Представлены к обсуждению результаты наиболее значимых исследований, посвященных ФДТ в нейроонкологии. Проведен анализ научных публикаций по данной тематике в базах данных Pubmed, EMBASE, Cochrane Library и eLibrary, опубликованных в промежуток времени с января 2000 г. по декабрь 2022 г. Найдено 204 публикации в зарубежных источниках и 59 публикаций в отечественных изданиях, в которых рассматриваются вопросы применения ФДТ в нейроонкологии. Анализ литературы показал, что в клинической практике интраоперационная ФДТ в нейроонкологии является важным инструментом, способствующим увеличению радикальности операции и локального контроля. Фундаментальное обоснование эффективности ФДТ заключается в изучении путей, ведущих к полной девитализации злокачественной опухоли, изучении механизмов локального

и системного иммунного ответа. При этом субклеточные мишени при ФДТ обусловлены свойствами фотосенсибилизаторов (ФС). В многочисленных исследованиях показана противоопухолевая эффективность использования ФДТ с ФС на основе хлорина е6, 5-аминолевулиновой кислоты, производных порфиринов. Установлены механизмы действия и мишени этих ФС. В России в ряде исследований подтверждена клиническая эффективность ФДТ у групп нейроонкологических пациентов с глиальным опухолями и вторичными метастатическими опухолями, однако до сих пор метод не включён в клинические рекомендации по оказанию высокотехнологичной нейрохирургической помощи. Безусловно, необходима дальнейшая разработка методики ФДТ в нейроонкологии, особенно у пациентов с высоким риском рецидива и агрессивными опухолями ЦНС.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, фотодитазин, 5-аминолевулиновая кислота, нейроонкология, менингиома, глиобластома, метастазы, рецидив, апоптоз, некроз.

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Ссылка для цитирования: Олюшин В.Е., Куканов К.К., Нечаева А.С., Скляр С.С., Вершинин А.Э., Диконенко М.В., Голикова А.С., Мансуров А.С., Сафаров Б.И., Рында А.Ю., Папаян Г.В. Фотодинамическая терапия в нейроонкологии // Biomedical Photonics. – 2023. – Т. 12, № 3. – С. 25–35. doi: 10.24931/2413–9432–2023–12–3-25–35.

Introduction

One of the most challenging tasks in oncology is the treatment of malignant tumors of the central nervous system (CNS). The average life expectancy of such patients after surgery, even with adjuvant therapy, is, on average, 14 months for glioblastoma multiforme and 25 months for anaplastic astrocytoma. Despite the successes of recent decades in understanding the fundamental principles of the mechanisms of neurooncogenesis, over the past 30 years the average life expectancy of patients has increased by only 2–4 months [1-3]. That is why it is necessary to develop alternative methods of treating neuro-oncology patients.

The study and development of photodynamic therapy (PDT) techniques for the treatment of malignant brain tumors in the Russian Federation began at the Russian Neurosurgical Research Institute (RNSI) named after. prof. A.L. Polenov back in 2001, where the foundations were laid and the first patents were obtained, and a protocol for the use of PDT in patients with glial tumors was developed [4, 5].

Outside the Russian Federation, research on the use of PDT in neuro-oncology began back in the 1990s [6]. However, at the moment, in many countries, the use of PDT for the treatment of malignant brain tumors remains within the framework of research activities. An exception is Japan, where since September 2013, PDT has been approved as a new and effective technique for increasing the degree of radicalization of surgical treatment of malignant glial tumors and has been included in the standards of medical care [7]. There are also literature data on the effectiveness of intraoperative PDT in the treatment of malignant meningiomas (median survival is reported to reach 23 months), however, reports are rare and patient groups are small [8].

In our opinion, at the present stage of development of the subject and further progress in PDT technology in neuro-oncology, the relevant directions are: minimizing the effect on healthy tissue, developing new generations of photosensitizers (PS), optimizing routes for delivering PS to target points, and developing new fiber-optic technologies. The main goal of this work is to present the current state and degree of development of intraoperative PDT in neuro-oncology based on the analysis of domestic and foreign literature, and to discuss the results of the most significant studies on PDT. The review examines the principles, advantages and disadvantages of PDT in the structure of complex treatment of malignant brain tumors, types of PS and methods of its delivery to the central nervous system, modern fiber-optic technologies in PDT, and demonstrates possible directions for further development of PDT technology in neuro-oncology.

The search of the studies published from January 2000 to December 2022 was performed in the Pubmed, EMBASE, Cochrane Library and eLibrary databases, using the query “photodynamic*[ti] AND therapy*[ti] AND (brain tumor* [ti] OR gliom*[ti] OR glioblastoma*[ti] OR meningiom*[ti] OR brain metast*[ti])” for foreign works and the keywords “photodynamic therapy AND (glioblastoma* OR gliomas* OR meningiomas* OR brain OR intracerebral metastases*)” for domestic ones. During the search, duplicate articles in different databases have been excluded, only peer-reviewed publications, excluding abstracts and publications based on conference proceedings, have been included.

204 publications were found in the Pubmed, EMBASE, and Cohrane Library databases, of which 26 were review articles, and only 2 systematic reviews that met the requirements of the international PRISMA system. In the eLibrary database, issues of PDT in neuro-oncology are discussed in 59 publications. This work analyzes literature data from both foreign and domestic authors.

Photosensitizers

Photosensitizers (PS) are one of the three main components of PDT. Properly selected PSs must meet a number of requirements, including the absence of systemic toxicity, selective accumulation in tumor tissue and acti-

vation at light wavelengths sufficient for deep penetration into brain tissue, minimal exposure to surrounding brain tissue, ease of administration of the drug into the patient's body, and clear visible fluorescence when visually assessing the degree of PS accumulation [9].

According to the publications, there are three generations of photosensitizing compounds [10, 11]. The molecules of the first generation of PS (photofrin, temoporfin, verteporfin) consist of naturally formed porphyrins, including hematoporphyrin (HpD). These compounds are activated at wavelengths of about 400 nm [12]. First generation PS drugs have a number of significant disadvantages: first, they have a low quantum yield of singlet oxygen, and as a result, lower efficiency; second, they realize their effect at wavelengths close in spectrum to natural light, having a pronounced phototoxic effect on the skin. First-generation PSs have a longer half-life of the drug compared to next-generation PSs [13].

In neuro-oncology, second-generation PSs are most often used, such as chlorins (photoditazin, photoran) and aminolevulinic acid derivatives (alasens). These drugs are activated by wavelengths of more than 600 nm and are most effective in generating singlet oxygen species [14, 15]. Recently, borated derivatives of porphyrins and chlorins have been actively studied in connection with the prospect of their use in PDT. The ability of borated derivatives of chlorin e6 and porphyrin (which are mono-, di- or tetraanions) to penetrate flat bilayer lipid membranes has been studied [16]. The advantage of these drugs is the accumulation of PS mainly in the mitochondria of tumor cells, which requires less light energy and minimizes side effects to almost zero. However, these drugs are more expensive and are yet used in experiments [15-17].

Today, active development of the third generation FS is underway. There are three main groups of third-generation PSs, namely, nanotechnological (nanoparticles, mesoporous structures, etc.), genetically engineered and carrier-conjugated (antibodies against tumor antigens, liposomes, vesicles). A number of studies have shown that third-generation PSs conjugated to specific carriers are characterized by the most pronounced specificity and tropism for malignant tumor tissues. For example, neuropilin-1 (receptor for endothelial growth factor) is overexpressed in glioblastoma and is involved in tumor neoangiogenesis. Conjugation of PSs with an antibody to neuropilin-1 provides a targeted effect on the tumor and also reduces blood flow in the tumor by approximately 50% [18].

Conjugation of PSs with an antibody to neuropilin-1 can increase the uptake of PS by tumor cells. In 2020, A. K. Rajora's et al. used apolipoprotein E3 nanoparticles (the E3 chaperone for cholesterol transit in the brain communicates with low-density lipoprotein receptors in glioblastoma cells) to facilitate the delivery of PS to tumor tissue [19].

M.A. Shevtsov et al. (2022) demonstrated that the membrane-bound protein mHsp70 is present in glioblastoma tumor cells but not in healthy cells. The authors have developed a drug based on an antibody to mHsp70 – the RAS70 peptide conjugated with PS, which will allow it to be used in the future for intraoperative fluorescence diagnostics, and possibly for PDT [20, 21].

Methods for delivering photosensitizers to the brain

The optimal method of drug delivery should be safe, minimally invasive, easy to learn and use. The main and alternative routes of drug delivery to the brain currently used are direct introduction of the active substance into tumor tissue, installation of an implantable pump system, use of devices for drug delivery with temporary disruption of the integrity of the blood-brain barrier (BBB), as well as transnasal, intravenous and oral administration of drugs [18, 22]. The intravenous route of administration has a number of obvious advantages, but faces the problem of molecules of active substances crossing the BBB [18]. Recent scientific advances offer opportunities to overcome such limitations with varying degrees of effectiveness. One of the possible solutions to this issue seems to be the use of phonophoresis. Ultrasound has demonstrated the potential to deliver drugs non-invasively across the BBB precisely to the desired area [22]. The use of targeted nanoparticles makes it possible to create the required drug concentration and reduce delivery time by improving the solubility and bioavailability of hydrophobic drugs [23].

In addition to the BBB, an obstacle to the delivery of drugs to the tumor is its heterogeneous and dynamically changing microenvironment. It is known that the microvasculature in glial tumors has a permeability of 7 to 100 nm, which is significantly less than that of tumors of other localizations (380-780 nm). To solve this problem, scientists propose using viruses that act as vectors that deliver the agent of interest [24]. Recently, in molecular medicine there has been increased interest in the use of quantum dots (nanomaterial with specific spectral characteristics), which have unique optical properties that provide high sensitivity and selectivity [25]. Another possible promising solution may be the use of magnetic nanoparticles [26]. Gold nanoparticles coated with covalent glycans, complementary to the cerebral vascular endothelium, have shown great potential for the delivery of therapeutic agents to the central nervous system [27, 28].

Fiber-Optic Technologies

When performing PDT, light of a certain wavelength and high intensity is required. Absorption of light quanta by PS molecules in the presence of oxygen leads to photochemical reactions (reactions of types I and II). Figure 1 shows a diagram of the reactions that occur during PDT.

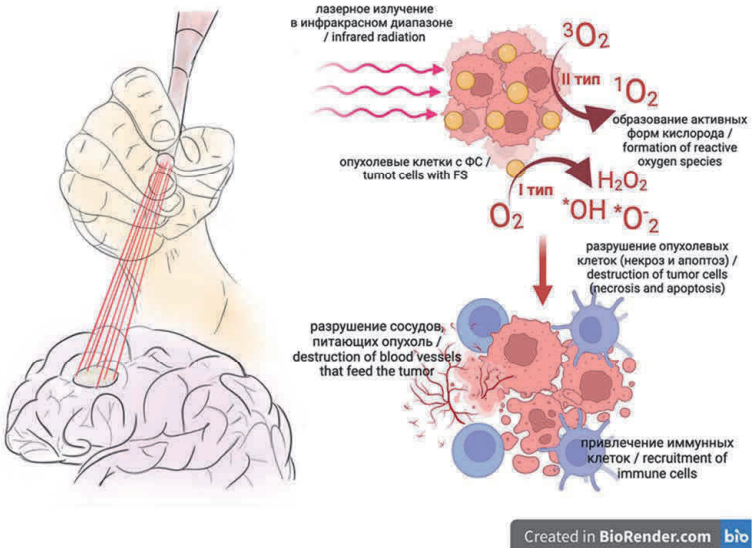

Рис. 1. Схематическое изображение реакций, происходящих при проведении фотодинамической терапии (ФС – фотосенсибилизатор).
Fig. 1. Scheme of the course of the reaction in photodynamic therapy (PS – photosensitizer).

Shown schematically in Fig. 1 singlet forms of oxygen cause cell death through the mechanisms of necrosis and apoptosis [29-32]. Both types of reactions occur simultaneously, and their effect ratio depends on the oxygen concentration in tissues, the pH of the environment and the composition of the substances used [33]. Carrying out PDT on the bed of a removed tumor increases the radicality of the operation, since the depth of light penetration, according to various studies, ranges from 5 to 12 mm [34-36]. The effectiveness of PDT, as well as its cytotoxicity, is influenced by many factors, including the type of PS, the administered dose of PS and light dose, as well as the presence of oxygen and the time interval between the administration of PS and exposure to light [37, 38]. It is known that tumor cells are often "hypoxic", and the main metabolic pathway is anaerobic glycolysis, which is problematic since PDT requires triplet O_2 in the ground state. In order to solve this problem at A.L. Polenov RNSI proposed creating controlled hyperoxia by increasing the partial pressure of oxygen in the oxygen-air mixture to 60%, which increases the formation of singlet oxygen (patent No. 2318542 dated March 10, 2008) [5].

In the work of D. Bartusik-Aebisher et al. (2022) the authors proposed a singlet oxygen generator based on the fiber-optic method for its targeted delivery during PDT. The goal of the idea is to develop a heterogeneous device for PDT that uses optical excitation of PS molecules released from the porous ends of a hollow microstructured optical fiber through which O_2 is supplied [39]. The essence of the work is to develop a methodology for bonding porous silicon to a commercially available hollow microstructured optical fiber, optimizing the optical coupling between the fiber and the bound PS, maintaining porosity throughout the bound silicon, and releasing the PS from the silicon matrix by irradiation with visible light.

The modern principle of PDT is the use of a single source of laser radiation, which is simultaneously used for photodiagnosis and PDT (the principle of phototheranostics), thereby ensuring spectroscopic monitoring of changes in the fluorescence intensity of the PS during laser irradiation. This achieves real-time PDT dose control, which leads to a therapeutic dose of light in the desired area and reduces photocytotoxicity to healthy tissues [40].

Clinical effectiveness

Many studies have shown the clinical effectiveness of surgical tumor resection in combination with PDT [41]. The article by W. Stummer et al. (2008) described a case of treatment of a patient with glioblastoma multiforme of the left frontal lobe who underwent surgical treatment with radiotherapy and chemotherapy. Twelve months after tumor resection, tumor recurrence was detected, and PDT was performed during re-resection. After oral administration of 5-ALA at a dosage of 20 mg/kg, irradiation was performed using a diode laser with a wavelength of 633 nm (with a power of 200 mW/cm^2) in continuous mode (light dose was 1200 J/cm^2). Subsequently, the patient lived for 5 years without tumor recurrence [42, 43]. C. Schwartz et al. (2015) in their study described a group of 15 patients who underwent PDT with 5-ALA at a dose of 20 or 30 mg/kg. Irradiation was carried out with a diode laser with a wavelength of 633 nm, the average light dose was 12.960 J. Patient survival was compared with the survival of patients who underwent only surgical resection of the tumor. Patients who underwent PDT showed a longer median disease-free survival, which reached 16 months, while in the second group this indicator was 10.2 months ($p < 0.001$). In 6 patients in the PDT group, the duration of recurrence-free survival was more than 30 months.

Seven out of fifteen patients were diagnosed with complications in the postoperative period, namely, transient aphasia and pulmonary embolism [44].

In the study by A.Yu. Ryndy et al. (2023) included 161 patients with a malignant glial tumor of supratentorial localization, of which 80 patients underwent PDT using photoditazine (1 mg/kg). The drug was administered intravenously during the induction of anesthesia. To irradiate the removed tumor bed, a Latus laser unit (ATKUS LLC, St. Petersburg) with a power of 2.5 W and a wavelength of 662 nm was used. Irradiation was carried out in a continuous mode, the duration of therapy depended on the area of the bed at the rate of a therapeutic light dose of 180 J/cm^2. The authors of the work proved that PDT as part of complex therapy for malignant gliomas of the brain significantly increases the median overall survival in patients with grade 4 gliomas – up to 20.7 ± 4.7 months (comparison group – 13.5 ± 2.3 months; p =0.0002); and also increases the median life expectancy without recurrence for patients with grade 3 gliomas – up to 21.7 ± 3.4 months (main group – 15.8 ± 3.1 months; p = 0.0002), and with grade 4 gliomas – up to 11.1±2.1 months (comparison group – 8.0±2.3 months; p=0.0001) [45].

The team at the Royal Melbourne Hospital has the largest clinical experience in the use of PDT in neuro-oncology, having studied more than 350 patients with gliomas. The authors used hematoporphyrin derivatives as PS at a dosage of 5 mg/kg (intravenous administration). The light dose ranged from 70 to 240 J/cm^2. In patients whose treatment regimen included PDT, 2-year survival rates for newly diagnosed and recurrent gliomas were 28% and 40%, respectively, and 5-year survival rates were 22% and 34%, respectively [46]. Regarding the side effects of PDT, as reported by S. Eljamel (2010), out of 150 patients who underwent PDT using 5-ALA and Photofrin, complications were identified in 7 patients: 3 (2%) patients developed deep vein thrombosis during treatment with Photofrin, none with 5-ALA-mediated PDT; 2 (1.3%) patients developed skin photosensitivity due to poor light protection in the summer months (0.6% with Photofrin-mediated PDT). After PDT, 2 (1.3%) patients developed cerebral edema requiring treatment, and one (0.1%) patient developed skin necrosis and wound liquorrhea from a previously irradiated skin flap [47]. Additional information about the use of various PSs and the clinical effectiveness of PDT in neuro-oncology is presented in Table.

Таблица
Сводные сведения о клинической эффективности ФТД в нейроонкологии
Table
Summary of clinical effectiveness of FTD in neurooncology

Автор, год Authors, publication year	Число пациентов Number of patients (n)	ФС, дозировка (мг/кг) PS, dose (mg/kg)	Доза света, (Дж/см^2) Light dose, (J/cm^2)	Нежелательные реакции при и после ФДТ (да/нет) Undesirable reactions during and after PDT (yes/no)	Медиана общей выживаемости (мес) Overall survival median, (months)
Хлорины Chlorins					
S. Stylli, 2005 [48]	78	Фотофрин I 5 мг/кг Photofrin I 5 mg/kg	70–240	Нет No	14,3
H. Kostron, 2006 [49]	26	Фоскан 0,15 мг/кг Foscan 0,15 mg/kg	20	Нет No	8,5
P.J. Muller, 2006 [50]	43	Фотофрин II 2 мг/кг Photofrin II 2 mg/kg	120	Нет No	11
Y. Muragaki, 2013 [51]	13	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	24,8
J. Akimoto, 2019 [52]	74	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	25

А.Ю. Рында, 2023 [45]	80	Фотодитазин 1 мг/кг Fotoditazin 1 mg/kg	180	Нет No	29,9
K. Shimizu, 2018 [53]	17	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	Не указана No data
M. Nitta, 2018 [54]	30	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	17,5
Tatsuya Kobayashi, 2022 [55]	70	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	16,0
C.W Teng, 2020 [56]	78 (крысы)	Нанокластеры цианина и хлорина 1 мг/кг Cyanine and chlorin nanocluster 1 mg/kg	30	Нет No	14,3
T. Maruyama, 2016 [57]	27	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	24,8
E.I. Kozlikina, 2020 [58]	1	Талапорфин натрия 40, мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	14,5
A. H. Sara, 2015 [59]	30	Фотолон 4 мг/кг Fotolon 4 mg/kg	30	Нет No	15,0
J. Akimoto, 2016 [60]	27	Талапорфин натрия 2 мг/кг Talaporfin sodium 2 mg/kg	27	Нет No	24,8
		Порфирины Porphyrins			
W. Stummer, 2006 [61]	122	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	100	Нет No	15,2
S. W. Cramer, 2020 [62]	350	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	80-120	Нет No	16,1
S. Schipmann, 2020 [63]	30	5-АЛК, 20 мг/кг 5-ALA, 20 mg/kg	100	Нет No	12,1
W. Stummer, 2008 [64]	1	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	100	Нет No	56
C. Schwartz, 2015 [65]	15	5-АЛК 30 мг/кг 5-ALA 30 mg/kg	12,9	Нет No	32,4
K. Mahmoudi, 2019 [66]	10	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	80	Нет No	18,9

ФС – фотосенсибилизатор; ФДТ – фотодинамическая терапия; 5-АЛК – 5-аминолевулиновая кислота.
PS – photosensitizer; PDT – photodynamic therapy; 5-ALA – 5-aminolevulinic acid.

Discussion

In neuro-oncology, the high rate of recurrence of malignant tumors is due to both the invasive type of tumor growth and its cellular resistance to traditional methods of adjuvant therapy [67, 68]. The cascade mechanisms that arise as a result of PDT cause alteration of cell membranes and lead to irreversible damage and destruction of photosensitized tumor cells. PDT not only directly affects tumor cells, but also reduces the vascularization (blood supply) of the tumor, causing an inflammatory response that stimulates a local and even systemic immune response. PDT does not affect the extracellular matrix, therefore, the tissue healing process is associated with a minimal risk of scar formation and adhesions, and the risk of infectious complications is reduced [66]. PDT is the subject of intensive research, although it has not yet become widespread in neuro-oncology, and only a few laboratories in the Russian Federation have transitioned it to clinical use [69–76].

PDT has been successfully used for more than two decades, however, in our opinion, the following problems still remain unresolved:

- Further development of PSs with greater selectivity of accumulation in tumor cells and tissues is necessary;
- Problem of skin photosensitivity;
- Problem of hypoxicity of malignant tumors;

There are certainly a number of advantages that determine the relevance and provide incentive for the further development of PDT technology:

- Low concentration of "free" PS in the body and rapid elimination;
- Impact on tumor cells adjacent to vital functional areas of the brain that are inaccessible to surgery;
- Ability to adapt existing endoscopic and microoptical techniques with new fiber optic equipment.

The prospect for further development of the topic of PDT in neuro-oncology is the development of a hybrid fiber-optic software and hardware complex based on technologies used in various fields of modern science: organic synthesis, physics, photochemistry, nanotechnology and artificial intelligence.

Conclusion

Due to the high selectivity of action, PDT therapy is a very promising technique compared to classical treatment methods used in neuro-oncology. Despite sample size limitations and the small number of randomized controlled trials, available evidence suggests a positive effect of PDT on the survival of patients with glioblastoma compared with standard therapy.

The main advantage of the PDT method is its high efficiency and minimally invasive nature. The high selectivity of the effect on brain tumor cells during PDT, the possibility of spectroscopic control and objectification of the dynamics of PS accumulation during irradiation allows to speak of PDT as an effective method for local control of neoplastic processes in the brain, which in turn leads to a long recurrence-free period and improvement quality of life of neuro-oncological patients. This approach in modern neuro-oncology can be considered as an option of theranostics and has the right to be called "photodynamic theranostics".

The work was carried out within the framework of state assignment No. 123021000128–4 "Development of a new technology for the treatment of patients with secondary brain tumors and recurrent meningiomas".

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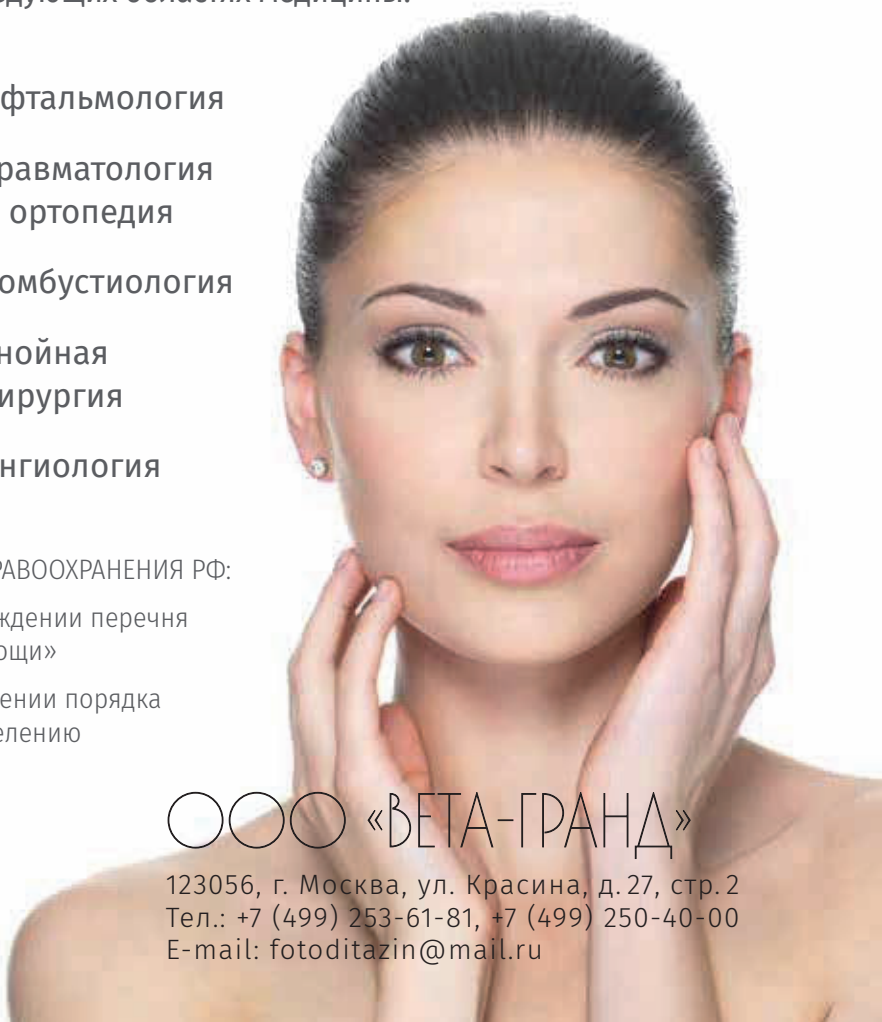

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