ORIGINAL ARTICLES

CLASSIFICATION OF INTRACRANIAL TUMORS BASED ON OPTICAL-SPECTRAL ANALYSIS

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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

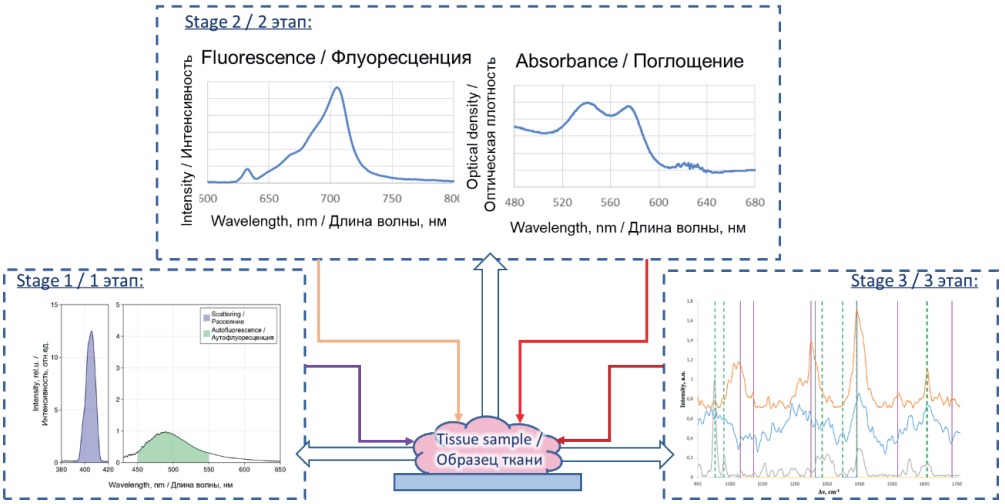

Рис. 1. Схема регистрации спектров флуоресценции, диффузного отражения и комбинационного рассеяния.
Fig. 1. Scheme for registering fluorescence, diffuse reflectance and Raman spectra.

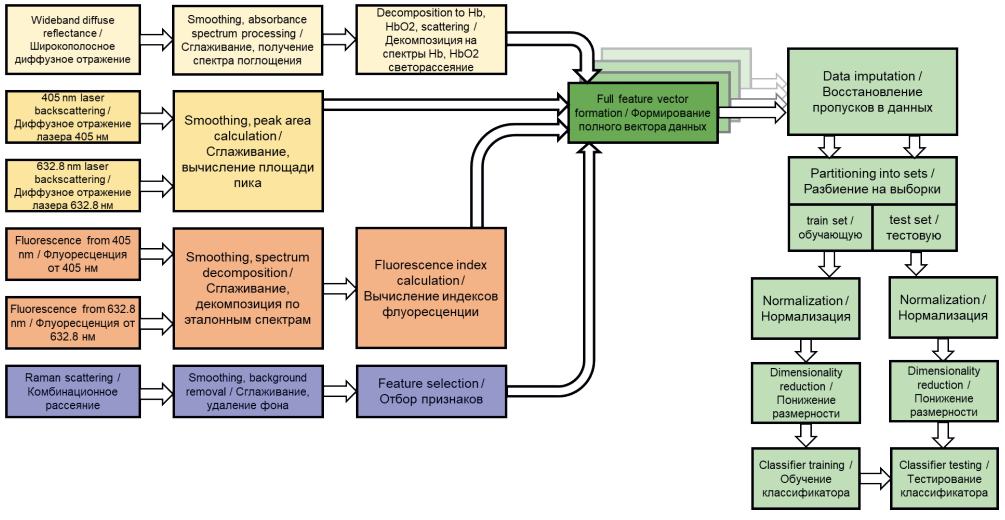

Рис. 2. Схема регистрации спектров, формирования вектора признаков и обучения классификатора.
Fig. 2. Scheme for spectra registration, feature vector generation and classifier training.

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

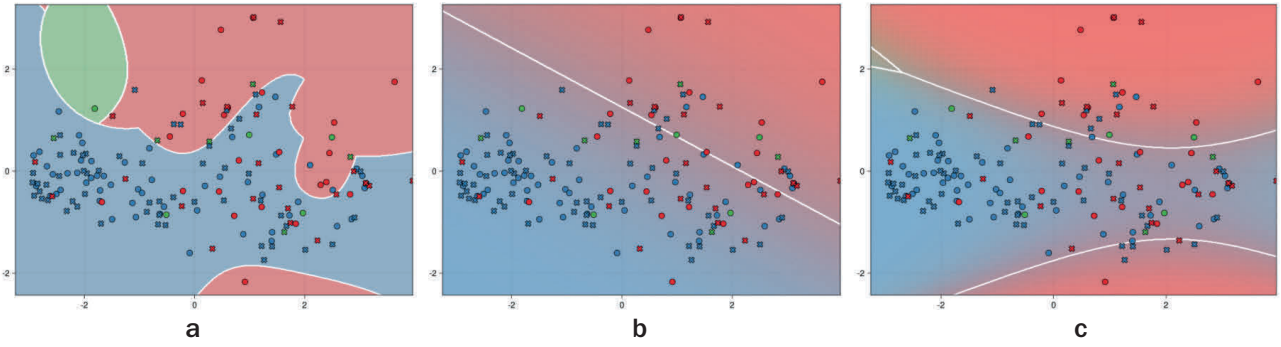

Рис. 3. Классификация образцов по диагнозам (красный – менингиомы, синий – глиомы, зеленый – метастазы) после применения PCA: a – метод опорных векторов; b – логистическая регрессия; c – наивный байесовский классификатор.
Fig. 3. Classification of samples by diagnosis (red – meningiomas, blue – gliomas,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

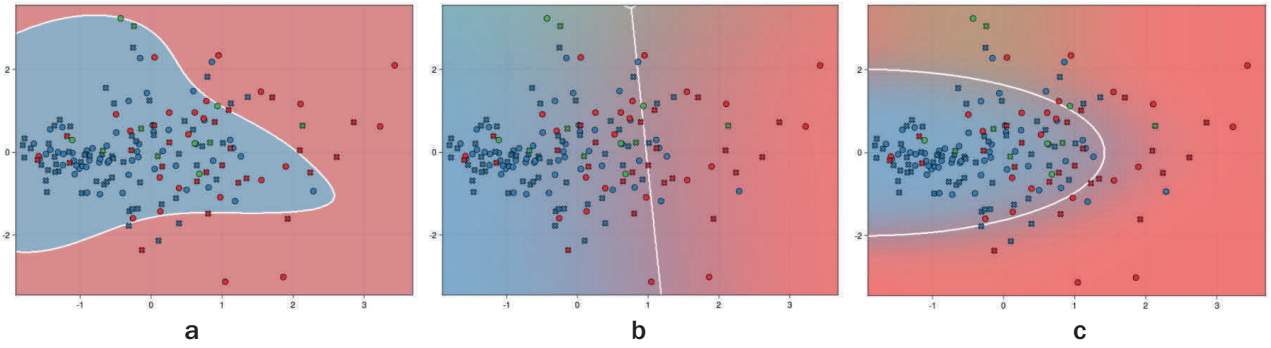

Рис. 4. Классификация образцов по диагнозам (красный – менингиомы, синий – глиомы, зеленый – метастазы) после применения LDA: a – метод опорных векторов; b – логистическая регрессия; c – наивный байесовский классификатор.
Fig. 4. Classification of samples by diagnosis (red – meningiomas, blue – gliomas,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

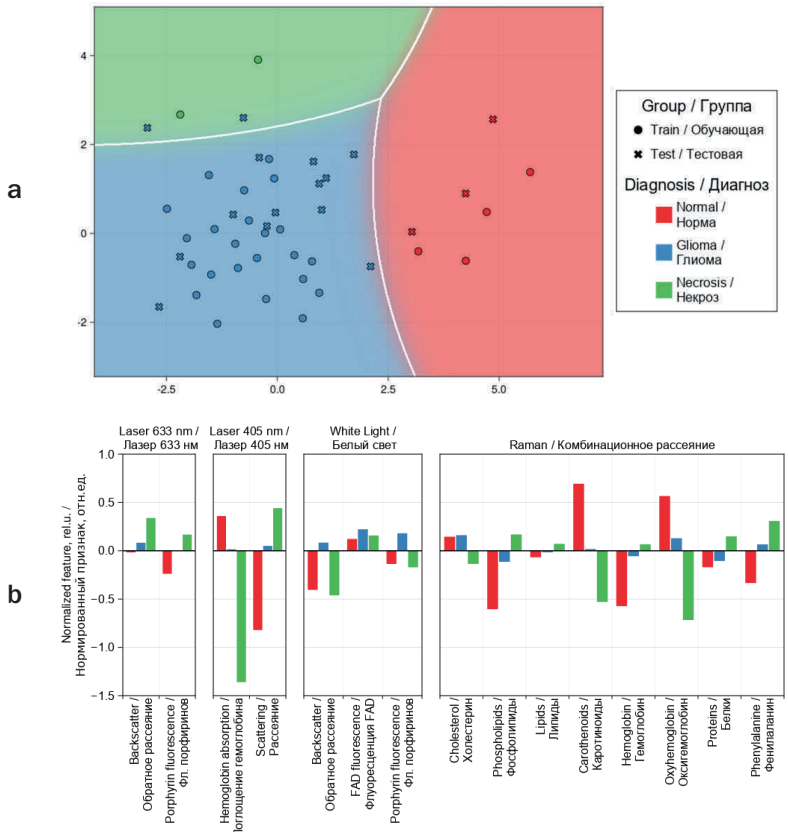

Рис. 5. a – Результаты классификации типов ткани глиом с использованием метода LDA и наивного Байеса, b – Средние нормированные значения признаков в классах в логарифмической шкале.
Fig. 5. a – Results of tissue type classification of gliomas using LDA and naïve Bayes, b – Mean normalized features in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