AUTOMATIZATION OF PLANNING AND CONTROL OF PHOTODYNAMIC THERAPY OF GASTROINTESTINAL ORGANS

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Abstract

The main aspects of automatization of photodynamic therapy (PDT) planning include several key areas related to improving accuracy, efficiency and personalization of treatment. Mathematical modeling of light propagation makes it possible to calculate the distribution of light energy in biotissues taking into account their optical characteristics and pathology geometry. At the same time the use of optical diagnostic methods allows not only to plan but also to control in real time the photodynamic effect with parameters adjustment depending on the degree of photosensitizer photobleaching and the hemoglobin oxygen saturation, as well as to determine the optical properties of tissues exactly in the exposure area. These methods also make it possible to personalize the effect, since it is based not on a priori information about averaged properties of organs and tissues, but on dynamically changing and measurable parameters. The use of photodynamic therapy for tumor diseases of the gastrointestinal tract has shown effectiveness as an adjunct to surgical treatment, as well as for tumors of small size and as a method of palliative treatment. At the same time from the point of view of light propagation in tissues the walls of gastrointestinal tract organs represent rather complex multilayer structures, optical properties of which depend on physiological state and pathologies developing in the organ. These circumstances make the task of automation of planning of photodynamic therapy of GI organs urgent and nontrivial. In this paper we review the methods that solve this problem.

Key words: photodynamic therapy, optical spectroscopy, photosensitizer, hemoglobin, optical properties, gastrointestinal tract

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АВТОМАТИЗАЦИЯ ПЛАНИРОВАНИЯ И КОНТРОЛЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ОРГАНОВ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Резюме

Основные аспекты автоматизации планирования фотодинамической терапии (ФДТ) включают несколько ключевых направлений, связанных с повышением точности, эффективности и персонализации лечения. Математическое моделирование распространения излучения позволяет рассчитать распределение световой энергии в биотканях с учетом их оптических характеристик и геометрии патологии. При этом использование оптических методов диагностики позволяет не только планировать, но и контролировать в реальном времени фотодинамическое воздействие с корректировкой параметров в зависимости от степени выгорания фотосенсибилизатора и степени насыщения гемоглобина кислородом, а также определять оптические свойства тканей именно в зоне воз-

действия. Эти методы обуславливают также и возможность персонализации воздействия, поскольку оно при этом основано не на априорной информации об усредненных свойствах органов и тканей, а на динамически меняющихся и измеряемых параметрах. Использование фотодинамической терапии для опухолевых заболеваний желудочно-кишечного тракта показало эффективность в качестве дополнения к хирургическому лечению, а также для опухолей небольшого размера и в качестве метода паллиативного лечения. При этом с точки зрения распространения света в тканях стенки органов желудочно-кишечного тракта представляют достаточно сложные многослойные структуры, оптические свойства которых зависят от физиологического состояния и развивающихся в органе патологий. Эти обстоятельства делают задачу автоматизации планирования фотодинамической терапии органов ЖКТ актуальной и нетривиальной. В настоящей статье проведен обзор методов, которые решают эту задачу.

Ключевые слова: фотодинамическая терапия, оптическая спектроскопия, фотосенсибилизатор, гемоглобин, оптические свойства, желудочно-кишечный тракт.

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Introduction

Photodynamic therapy (PDT) is a progressive method of treatment of various diseases, including malignant neoplasms [1, 2] and precancerous conditions [3] of the gastrointestinal (GI) organs. To implement photodynamic action, a combination of light-sensitive substances (photosensitizers) and light radiation of a certain wavelength is necessary. In this case, PDT can either directly form free radicals through a substrate (Type I) or generate singlet oxygen through the transfer of energy to oxygen (Type II). The effectiveness of PDT depends on personalized treatment planning and dosimetric control during the procedure, which necessitates the development and application of techniques to achieve these goals.

The main limitation of traditional PDT protocols is the standardized approach, which does not take into account the variability of tissue optical properties, the degree of photosensitizer accumulation and heterogeneity of biological tissues. This leads to the risk of damage to healthy tissues or insufficient therapeutic effect. For example, the absorbed dose varies depending on the light penetration depth and the local concentration of the photosensitizer. The absorbed dose is mainly determined by the light power density, energy dose, photosensitizer and oxygen concentration in the irradiated tissue, which makes it necessary to take into account the optical properties of tissues and individual characteristics of patients [4]. Therefore, control of PDT by dosimetry and automatic treatment planning, as well as personalization of the procedure, are important factors to maximize the effectiveness of therapy. Fig. 1 presents a scheme showing the sequence of dosimetric techniques applied during the photodynamic therapy procedure.

Personalization of PDT is carried out by adapting the radiation dose and exposure time to the specific biological characteristics of the patient. This review is devoted to the consideration of existing methods of automated planning of photodynamic treatment and various techniques of

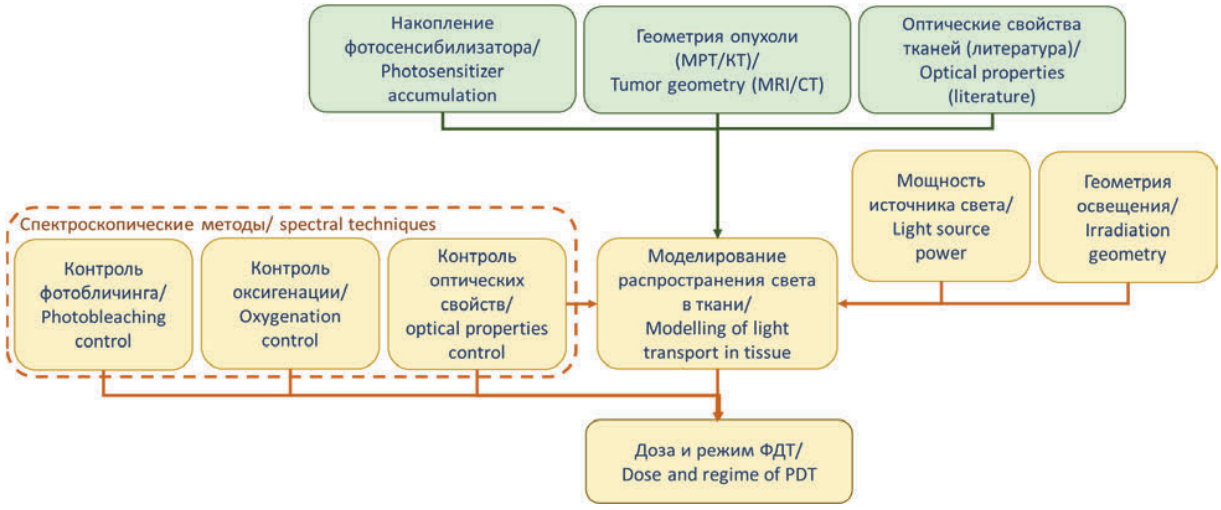

Рис. 1. Последовательность процесса дозиметрического контроля ФДТ.
Fig. 1. Sequence of the process of dosimetric control of PDT.

dosimetric control, as well as the influence of taking into account the optical properties of exposed biological tissues on the effectiveness of treatment.

Review of PDT methodology for GI organs

In this paragraph we provide an analysis of the methodology of photodynamic therapy on gastrointestinal organs, the key aspects of which are summarized in two tables, with Tab. 1 shows the studies for which the method of PDT efficacy control was not specified in the papers, and in Tab. 2 are those for which the efficacy control was performed. Tab. 1 includes data from 34 studies, and Tab. 2 nine, so we can conclude that only every fifth PDT protocol for gastrointestinal neoplasms is accompanied by a control procedure.

Tables 1 and 2 compare different methodologies of photodynamic therapy of various diseases of gastrointestinal tract organs. In some works instead of dose (J/cm^2) and power (W/cm^2) per unit area the dose per unit diffuser length (J/cm) and power per unit diffuser length (W/cm) are given. These values are convenient for certain applications, but for comparing studies using different photosensitizers and illumination geometries, the values per unit area are more informative because they provide information on the absolute measure of light illuminating the surface of the area being treated [45]. One of the most common pathologies for which this treatment method is used is Barrett's esophagus also abbreviated CELLO (columnar epithelium lined lower oesophagus). In this disease in the epithelial lining of the esophageal mucosa is found atypical for the normal intestinal type epithelium instead of flat multilayer epithelium. If untreated, Barrett's esophagus can progress to the malignant pathology of adenocarcinoma, which has the fastest growing incidence of any solid tumor in most of the world [62]. When treatment is performed according to standardized protocols that do not take into account the tissue characteristics of a particular patient, there is variability in the response to PDT, in the case of Barrett's esophagus it consists of residual Barrett's syndrome and stricture formation. One of the reasons for the different outcome of therapy is the difference in the delivered dose, as the actual dose of light absorbed by tissue depends not only on the energy of light, but also on the optical properties and geometry of the sample, which is especially significant for hollow organs [46] and, consequently, for GI organs. Accordingly, in order to increase the probability of a positive treatment outcome, it is necessary to carry out personalized laser-induced exposure depending on the tissue characteristics of each specific patient. This task can be accomplished using methods of automatic planning and dosimetric measurements directly during the PDT procedure.

Таблица 1.
Сопоставление протоколов проведения фотодинамической терапии различных заболеваний желудочно-кишечного тракта – без контроля эффективности

Table 1.
Comparison of protocols for photodynamic therapy of various gastrointestinal diseases – without effectiveness control

№	Источник Source	Диагноз Diagnosis	Фотосенсибилизатор Photosensitizer	Длина волны (нм) Wavelength (nm)	Вид облучателя The type of light delivery	Доза (плотность мощности) Energy (fluence rate)
1	[1]	КРР CRC	Фотофрин Photofrin	630	ПТ FC	200 J/cm^2 (-)
2	[2]	АП EA	Фотофрин Photofrin	630	ЦД CD	300 J/cm (400 mW/cm)
3	[3]	ПБ, АП CELLO, EA	Фотофрин Photofrin	632	ЦД CD	150-250 J/cm (400 mW/cm)
4	[5]	ПБ CELLO	Фотофрин Photofrin	630	ЦД, баллон CD, balloon	130 J/cm (400 mW/cm)
5	[6]	ПБ, АП CELLO, EA	Фотофрин, 5-АЛК Photofrin, 5-ALA	630	ЦД, баллон CD, balloon	50 – 75 J/cm (400 mW/cm)
6	[7]	ПБ, АП CELLO, EA	Фотофрин Photofrin		ЦД CD	150 – 225 J/cm (-)
7	[8]	ПБ, АП CELLO, EA	Фотофрин II, ПГП Photofrin II, HPD	630	ЦД CD	200 J/cm, 32 J/cm^2 (400 mW/cm)
8	[9]	ПБ CELLO	Фотофрин Photofrin	630	ЦД CD	150 J/cm (-)
9	[10]	ПБ CELLO	5-АЛК, фотофрин 5-ALA (a), photofrin (b)	635	(a): ПТ, (b): ЦД (a): FC, (b): CD	(a): 200J/cm^2 (b): 130 J/cm, 28 J/cm^2 (-)
10	[11]	ПБ CELLO	5-АЛК 5-ALA	635	ЦД CD	500-1000 J/cm

11	[12]	ПБ, АП CELLO, EA	5-АЛК 5-ALA	635	ПТ FC	150 J/cm^2 (100 mW/cm^2)
12	[13]	ПБ, АП CELLO, EA	5-АЛК 5-ALA	630	ЦД CD	100 – 200 J/cm^2 90 – 150 mW/cm^2
13	[14]	АП EA	5-АЛК 5-ALA	580 – 720, 1250 – 1600	ПТ FC	100 J/cm^2 (-)
14	[15]	ПБ CELLO	mTHPC	514	ЦД CD	75 J/cm^2 (100 mW/cm^2)
15	[16]	ПБ CELLO	mTHPC	511 (a), 652 (b)	ЦД CD	(a): 75 J/cm^2 (b): 7 J/cm^2 (60-100 mW/cm^2)
16	[17]	АП, РП EA, ESCC	5-АЛК (a), mTHPC (b) 5-ALA (a) mTHPC (b)	635, 652	ЦД, баллон CD, balloon	(a): 150J/cm^2, (b): 20 J/cm^2 100 mW/cm
17	[18]	ПБ, АП CELLO, EA	mTHPC	652	ЦД CD	8 – 20 J/cm^2 (200 mW/cm)
18	[19]	ОП ET	Фотофрин Photofrin	630	Волокно с микролинзой Microlens fiber	75 J/cm^2 (-)
19	[20]	ОП ET	Фотофрин, талапорфин натрия Photofrin, talaporfn sodium	630, 664	ПТ FC	75-100 J/cm^2 (150 mW/cm^2)
20	[21]	ОП ET	Талапорфин натрия Talaporfin sodium	664	-	100 J/cm^2 (-)
21	[22]	АП EA	HPPH	665	ЦД CD	150-175 J/cm (100- 400 mW/cm^2)
22	[23]	РП ESCC	Фотофрин Photofrin	630	ПТ, микролинза, ЦД FC, microlens, CD	75 J/cm^2 (-)
23	[24]	РП ESCC	Фотофрин Photofrin	630	Волокно с микролинзой Microlens fiber	75 J/cm^2 (160 mW/cm^2)
24	[25]	ОП ET	Талапорфин натрия Talaporfin sodium	664	ПТ FC	50 J/cm^2 (150 mW/cm^2)
25	[26]	ОП ET	Фотофрин Photofrin	630	Баллон Balloon	100 J/cm (-)
26	[27]	РП ESCC	Талапорфин натрия Talaporfin sodium	664	ПТ FC	100 J/cm^2 (150 mW/cm^2)
27	[28]	ПБ, АП CELLO, EA	Фотофрин Photofrin	630	ЦД CD	- (-)
28	[29]	ПБ CELLO	Фотофрин Photofrin	630	ЦД CD	100 – 200 J/cm (-)
29	[30]	ПБ, АП CELLO, EA	ПГП, фотофрин HPD, photofrin	630	ЦД CD	300 J/cm, 32 J/cm^2 (400 mW/cm)
30	[31]	РП ESCC	Фотофрин Photofrin	630	ПТ FC	75 J/cm^2 (-)
31	[32]	АП, РП EA, ESCC	Фотофрин Photofrin	630	ЦД CD	300 J/cm (400 mW/cm)
32	[33]	ОП ET	Фотофрин II Photofrin II	630	ЦД CD	300 – 400 J/cm (-)
33	[34]	ПБ CELLO	ПГП, фотофрин HPD, photofrin	630	ЦД, баллон CD, balloon	200 J/cm (400 mW/cm)
34	[35]	РЖ GC	Фотофрин, талапорфин натрия Photofrin, talaporfin sodium	405, 630	ПТ FC	60 J/cm^2 (150 mW/cm^2) 60 J/cm^2

КРР – колоректальный рак, АП – аденокарцинома пищевода, ОП – опухоли пищевода, ПБ – пищевод Баретта, РП – плоскоклеточный рак пищевода, РЖ – рак желудка, ПГП – производные гематопорфирина, 5-АЛК – 5-аминолевулиновая кислота, hTHPC – 5,10,15,20-тетра(м -гидроксифенил)хлорин, HPPH (2-[1-гексилоксиэтил]-2-девинил пирофеофорбид-а), ЦД – цилиндрический диффузор, ПТ – плоский торец.
CRC – Colorectal Cancer, EA – Esophageal Adenocarcinoma, ET – Esophageal Tumors, CELLO – Columnar Epithelium Lined Lower Oesophagus, ESCC – Esophageal Squamous Cell Carcinoma, GC – Gastric Cancer, HPD – Hematoporphyrin Derivatives, 5-ALA – 5-aminolevulinic acid, hTHPC – 5,10,15,20-tetra(m-hydroxyphenyl)chlorin, HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a), CD – Cylindrical Diffuser, FC – Flat Cut.

Таблица 2.
Сопоставление протоколов проведения фотодинамической терапии различных заболеваний желудочно-кишечного тракта с контролем эффективности

Table 2.
Comparison of protocols for photodynamic therapy of various gastrointestinal diseases with monitoring of effectiveness

№	Источник Source	Диагноз Diagnosis	Фотосенсибилизатор Photosensitizer	Длина волны (нм) Wavelength (nm)	Вид облучателя The type of light delivery	Доза (плотность мощности) Energy (fluence rate)	Контроль эффективности Effectiveness control
1	[36]	ПБ CELLO	5-АЛК 5-ALA	635	CD, balloon	150 J/cm^2 (150 mW/cm^2)	Дозиметрия ФС, фотовыцветание Photosensitizer concentration, photobleaching
2	[37]	РЖ GC	5-АЛК 5-ALA	635	FC	- (30 W/cm^2)	Фотовыцветание Photobleaching
3	[38]	CRR	Фотофрин Photofrin	532	FC	- (-)	Сатурация, концентрация гемоглобина, концентрация ф/с Blood oxygenation, hemoglobin concentration, drug concentration
4	[39]	ПБ, АП CELLO, EA	Фотофрин Photofrin	630	CD	- (400 mW/cm)	Флуоресцентная спектроскопия Fluorescence spectroscopy
5	[40]	EC	Талапорфин натрия Talaporfin sodium	664	-	100 J/cm^2 (150mW/cm^2)	Визуализация оксигенации Oxygensaturation imaging
6	[41]	ПБ CELLO	5-АЛК 5-ALA	505	-	- (-)	Флуоресцентная спектроскопия Fluorescence spectroscopy
7	[42]	АП EA	5-АЛК 5-ALA	630	CD	100 – 200 J/cm^2 (90 – 150 mW/cm^2)	Флуоресцентная спектроскопия Fluorescence spectroscopy
8	[43]	ПБ CELLO	Фотофрин Photofrin	635	CD	37 J/cm^2 (45 mW/cm^2)	Допплеровская ОКТ Doppler OCT
9	[44]	ПБ CELLO	5-АЛК 5-ALA	630	CD	100 J/cm^2 (100 mW/cm^2)	Контроль мощности излучения Fluence rate measurements

КРР – колоректальный рак, АП – аденокарцинома пищевода, ПБ – пищевод Баретта, РЖ – рак желудка, 5-АЛК – 5-аминолевулиновая кислота, ЦД – цилиндрический диффузор, ПТ – плоский торец, ФС – фотосенсибилизатор.
CRC – Colorectal Cancer, EA – Esophageal Adenocarcinoma, CELLO – Columnar Epithelium Lined Lower Oesophagus, GC – Gastric Cancer, 5-ALA – 5-aminolevulinic acid, CD – Cylindrical Diffuser, FC – Flat Cut.

Automated planning of photodynamic therapy

Automating PDT planning addresses key challenges such as tumor irregularity, patient movements, and the need for accurate light dosimetry in complex anatomical areas, and includes several key components. First, computer-aided design algorithms determine the optimal placement, power, and configuration of light sources (e.g., fiber-optic probes or LED arrays) based on 3D imaging data (e.g., MRI or CT) to adjust the distribution of light absorption in tissues to the tumor shape and minimize the impact on organs at risk. Second, the automation of PDT planning usually implements dynamic dosimetry and light dose monitoring. Automated systems can adjust light output in real time to account for patient movement or changes in tissue optical properties. Third, machine learning techniques, which are now being widely adopted in clinical practice, are also being used for this task to adapt to individual variations in tissue optical properties, making treatment plans more reliable and personalized.

Automated planning of photodynamic therapy (PDT) uses advanced mathematical and technical methods to

optimize the light dose, minimize damage to healthy tissue, and maximize tumor destruction. PDT planning must take into account irradiation geometry, separating the cases of intrathecal and superficial irradiation schemes. Intrathecal PDT has evolved as a response to the clinical demand for therapy of deep-seated tumors, the effect on which is limited by the depth of light penetration during surface irradiation.

Modeling of light propagation is the main tool for estimating the absorbed light dose in tissues [47]. Monte Carlo methods numerically simulate light transport in three-dimensional models of pathologies, including complex geometry [48], in the volume of surrounding tissues, the geometric parameters of which are obtained using MRI or CT [49]. Dose-volume histograms derived from modeling reduce computational costs and allow iterative improvement of the plan. This modeling takes into account the optical properties of tissues (absorption, scattering), generates the distribution of the absorbed dose in the tissue volume for different illumination geometries, allows iteratively refining the position of sources and taking into account the change of optical properties during the PDT procedure.

The clinical implementation of these PDT planning techniques is represented, for example, by PDT-SPACE (open source software combining machine learning for planning that takes into account individual patient differences, adaptive optimization for bone metastases and brain gliomas, damage reduction (>70% compared to previous methods) while achieving >98% tumor destruction) [47]. The approach implemented in the FullMonte software package for tetrahedral 3-D Monte Carlo simulation, visualization, and analysis of light propagation in inhomogeneous turbid media is also of interest [50].

Analysis of oxygen concentration in the photodynamic treatment zone is another critical component of planning and implementation of photodynamic therapy (PDT), along with dosimetry of absorbed radiation, because the efficacy of PDT depends on the simultaneous presence of photosensitizer, light, and oxygen. The generation of cytotoxic reactive oxygen species (ROS), especially singlet oxygen, is central to the mechanism of PDT, and insufficient oxygen in tissues can limit therapeutic results [51]. Maintaining adequate oxygenation throughout treatment is essential for optimal ROS formation and exposure control. Monitoring methods are represented by several approaches. Direct measurement methods include oxygen electrodes and fluorescent optodes. They provide a direct, spot measurement of tissue partial pressure of oxygen (pO_2), but are invasive and not always suitable for clinical settings [51].

Optical spectroscopy also allows us to determine oxygen concentration indirectly, since it is closely related to the level of hemoglobin oxygen saturation. At the same time, this approach provides noninvasive assessment of oxygenation status and is the most widely used at present [51, 52].

Another important aspect of PDT planning that is often overlooked in clinical application is modeling of the biological response. It is necessary to take into account the dynamics of oxygen transport during PDT and singlet oxygen-mediated cell death kinetics [53], binary models of cell fate decision making [54].

The use of photodynamic therapy for tumor diseases of the gastrointestinal tract has shown efficacy as an adjunct to surgical treatment, as well as for tumors of small size and as a method of palliative treatment [55-57]. Consider in more detail such aspects of PDT planning automation as the use of mathematical models of treated organs and tissues for numerical simulation of light propagation in the medium and consideration of optical properties of these organs and tissues.

PDT control

The transition to personalized PDT dosimetry is a non-trivial task due to the difficulty in accounting for the nonlinear interaction between light dose, irradiation time, and the concentration of photosensitizer and molecular oxygen [58].

PDT dosimetry

The main three components of photodynamic therapy are photosensitizer, laser light and oxygen. Accordingly, in order to transition to personalized treatment, it is necessary to monitor the parameters related to these three components. PDT dosimetry can be divided into four types: explicit and implicit dosimetry, monitoring of biological tissue response, and direct dosimetry [59].

Explicit dosimetry takes into account the entire PDT pathway, from light absorption to singlet oxygen production. This type of dosimetry involves direct control of the power density of the light source, photosensitizer concentration, and oxygen content [60]. This type of dosimetry works well in conditions of high tissue oxygen saturation, when the PDT dose, which is proportional to the time integral of the product of local photosensitizer concentration and light flux intensity, is the most accurately defined dosimetric value and a good indicator of treatment outcome [61]. Using explicit dosimetry, initial PDT parameters are measured and incorporated into a dose calculation model to estimate singlet oxygen production [62]. Even under static conditions, it is technically difficult to measure all three parameters and, given that they are also dynamically interdependent, it is difficult to achieve accurate dose determination [62].

Taking into account the interdependence of light intensity, photosensitizer concentration, and oxygen content, the parameters controlled by direct dosimetry, is a difficult task in determining the photodynamic dose. The dependence of the photosensitizer decay on

the radiation intensity cannot be expressed as a simple exponential expression [63]. Since it is extremely difficult to track all changes using explicit dosimetry, implicit dosimetry is often used, which aims to measure a value that depends on all or at least most of the above factors [63].

Implicit dosimetry measures parameters that depend on several of the three components of PDT, such as photobleaching and photoproduct formation [64]. The main goal of implicit dosimetry is to quantify all relevant individual parameters, the aggregate of which can be represented as an integral parameter closely correlating with the therapeutic dose [65].

Monitoring the response of biological tissues involves adjusting the parameters of photodynamic treatment depending on its effect on the tissues of the treated organ, which is monitored by avoiding the occurrence of necrosis area or blockage of the vascular channel [66].

In order to control the PDT procedure using direct dosimetry, it is necessary to measure the presence and amount of reactive oxygen species in the tissues under study [67]. The technique is based on the assumption that the PDT effect is mainly achieved through photochemical reactions of the second type.

Currently, the main methods used for PDT dosimetry are optical imaging, including techniques based on fluorescent and diffusely reflected signal registration, and modeling [65]. A comparison of techniques for monitoring the effectiveness of PDT and types of dosimetry is shown in Table 3. Optical imaging is a broad concept that includes such techniques as video fluorescence imaging, fluorescence spectroscopy, optical diffusion spectroscopy (mainly in diffuse reflection geometry), Raman spectroscopy, and optical coherence tomography [65]. Video fluorescence imaging and fluorescence spectroscopy make it possible to determine the areas of photosensitizer accumulation, as well as to evaluate photobleaching. Accordingly, these methods can be referred to implicit dosimetry. Diffuse reflectance spectroscopy can be used to estimate oxygen content, which allows this method to be classified as explicit dosimetry. This method can also be used to determine the optical properties of tissues to personalize photodynamic treatment. Raman spectroscopy allows to determine the concentration of photosensitizer [68, 69], therefore, it is a method of explicit dosimetry. Optical coherence tomography [70] refers to methods of monitoring the response of biological tissues. Singlet oxygen dosimetry [71], which refers to direct dosimetry, is also used as a method to monitor photodynamic effects. It is also possible to use several techniques together, for example, diffuse reflectance spectroscopy and fluorescence spectroscopy [52, 72] or singlet oxygen photobleaching and luminescence measurements [62], for simultaneous monitoring of a larger number of parameters.

Таблица 3.
Сопоставление вида дозиметрии и методик контроля эффективности ФДТ

Table 3.
Comparison of the type of dosimetry and methods for monitoring the PDT effectiveness

Вид дозиметрии Type of dosimetry	Контролируемые параметры Controlled parameters	Методы Methods
Явная Explicit	Плотность энергии источника, концентрация фотосенсибилизатора, содержание кислорода Source energy density, photosensitizer concentration, oxygen content	Спектроскопия диффузного отражения Diffuse reflectance spectroscopy
Неявная Implicit	Фотобличинг или образование фотопродуктов Photobleaching or photoproduct formation	Флуоресцентная диагностика Fluorescent diagnostics
Контроль реакции биологических тканей Control of biological tissue reactions	Недопущение некроза и блокировки сосудистого русла Preventing necrosis and blockage of the vascular bed	Оптическая когерентная томография Optical coherence tomography
Прямая Direct	Количество активных форм кислорода Active oxygen forms	Люминесценция синглетного кислорода Singlet oxygen luminescence

Determination of optical properties as a method of PDT control

Regardless of the choice of the type of dosimetry for more accurate realization of PDT it is necessary to take into account the optical properties of tissues. When performing explicit dosimetry, this is possible by introducing a correction factor that allows taking into account the optical properties when recording fluorescence; this methodology is presented in [73]. In this paper, optical properties were determined not directly during photodynamic treatment, but beforehand using optical phantoms imitating biological tissues.

When calculating the required dose from the light source during photodynamic therapy, the dose that will be delivered to tissues is most often calculated. However, not the entire volume of this dose will be absorbed by biological objects, including due to incomplete overlap of the light source spectra and absorption of the photosensitizer [74]. Accordingly, for more accurate control of the PDT procedure, it is necessary to make measurements of the absorbed dose in each case. In addition to influencing the absorbed

dose, the optical properties of tissues also affect the spectral characteristics of the fluorescence signal, including the detectable signal depends on the oxygen concentration [75]. Consequently, determination of the optical characteristics of the studied objects is important not only for personalization of photodynamic therapy, but also for increasing the accuracy of fluorescence diagnostics.

The interaction of optical radiation with tissues can be described using various analytical models, including modified Beer-Lambert law [76], Jacques [77] and Yudovsky [78] models. Also, light propagation in tissues can be investigated using Monte Carlo simulations. In [79], a comparison of the three mentioned analytical models is presented with respect to their applicability for estimating tissue parameters. The comparison was carried out using data obtained by Monte Carlo simulation and measurements on optical phantoms with known optical properties. The simulation results are best matched by the Yudovsky model. The empirical data are closest to the calculations performed with the Jacques model.

There are various methods that allow to determine the optical properties of biological objects by processing the data obtained from spectral measurements. The most common are the inverse Monte Carlo method and the inverse addition-doubling method [80]. These techniques involve registration of spectra in several geometries. Conducting measurements of diffuse reflectance and transmittance spectra allows the determination of two parameters: absorption coefficient and reduced scattering coefficient. To recover three optical properties: absorption coefficient, scattering coefficient and anisotropy factor, it is necessary to register spectra in three geometries. Globally, modern algorithms for recovering optical properties of biological tissues are based either on integrating sphere measurements, which are based on reflectance and transmittance measurements of thin slices of dissected tissue [81], and techniques based on the registration of diffusely reflected signal using point sources and detectors [82-84], which aim to characterize the spatial, temporal, and spectral dependence of the recorded signal. The recovery of information about optical properties from measured signals can be based on empirical calibration based on tables with a representative set of reference phantoms with known characteristics [83], as well as on models with analytical approximation, such as diffusion theory [84], or Monte Carlo simulations [82]. Currently, data on optical properties have been obtained for such localizations as bone, nerve, muscle, and adipose tissue [85], white and gray matter of the brain [86], esophagus [87], stomach [88, 89], colon [90, 91], and small intestine [89]. In all the works cited in this paragraph, the optical properties were determined not during surgery.

Currently, several scientific groups are working on the task of taking into account the optical properties of tissues during clinical photodynamic treatment. They propose to take into account the optical properties of tissues during fluorescence registration by applying the Monte Carlo method for modeling the propagation of radiation in biological media, with the values of optical properties either determined using optical phantoms [92, 93] or taken from literature data [94].

The article [95] is devoted to the development and demonstration of a noninvasive method for quantitative determination of optical properties of turbid media (including biological tissues) in the wavelength range from 430 to 1050 nm. The method is called spatially modulated quantitative spectroscopy and is based on the measurement of reflected light from the sample under study when it is illuminated at different spatial frequencies. This allows to calculate absorption and scattering coefficients without preliminary assumptions about the composition of chromophores in the sample. The method was tested on liquid phantoms with known concentrations of absorbers and scatterers. The obtained values of optical properties had good agreement with the expected results. As a demonstration of the feasibility of the *in vivo* method, an experiment was performed on human skin. The obtained skin absorption spectrum was described with good accuracy using models taking into account the contribution of oxy- and deoxyhemoglobin, water and melanin, and the quantitative values of these components corresponded to the data for skin from literature sources.

The authors of the study [38] developed a technique for transforming the diffuse reflectance signal in a wide spectral range into parameters of human skin, such as light penetration depth, blood oxygen saturation, hemoglobin concentration, and epidermis thickness. The diffusion approximation of the radiative transfer theory was used to analyze the data. The obtained values of blood oxygen saturation and hemoglobin concentration are in good agreement with published physiological data, the epidermis thickness measured optically coincides with the results of histologic studies. The proposed approach can be used to monitor skin condition, diagnose diseases and evaluate the efficacy of photodynamic therapy.

In the article [96], modeling of photodynamic therapy of the esophagus was carried out taking into account the absorption and scattering coefficients determined by measuring a porcine esophagus sample on integrating spheres. PDT modeling was performed by Monte Carlo method taking into account tissue multilayers. The introduction of photosensitizer was taken into account by changing the values of optical properties: both absorption and scattering increased. The depth of tissue damage was determined for different values of light

dose. The obtained values were compared with clinical results in other literature sources.

In [97], the control of PDT efficiency was determined using fluorescence spectroscopy and light dose measurements. Depending on the *in vivo* determined concentration of the photosensitizer (Photofrin), a correction for the optical properties of the object under study was introduced. The method of correction of irradiation procedure depending on optical properties was developed by means of Monte Carlo simulation and tested on optical phantoms. The presented system allows simultaneous examination of eight areas in real time.

In [98], the determination of tissue optical properties is carried out to optimize the implicit dosimetry technique. The method consisted in measuring the fluorescence and reflected signal, which were used to estimate blood volume, reduced scattering coefficient and photosensitizer concentration. Validation of the methodology was performed on optical phantoms using least squares nonlinear regression analysis and *in vivo* on mice. Diffuse reflectance spectroscopy was used as a reference method to independently measure the properties of biological tissues and compare the results. The blood volume and scattering coefficient measured by the developed method were compared with the results obtained by diffuse reflectance spectroscopy. Hemoglobin oxygen saturation was also measured in the tumor using diffuse reflectance spectroscopy.

The work [99] is devoted to the application of machine learning methods (neural networks and gradient boosting regression trees) to restore the optical properties of biological tissues during intrathecal PDT in real time by adapting the power of light sources. Optical properties of tissues (absorption coefficient μ_a and scattering coefficient μ_s) can change during treatment due to changes in blood flow, edema or cell swelling, which affects the light dose distribution. Traditional methods to account for optical properties based on analytical models (e.g., diffusion approximation) are not accurate enough for deep-seated tumors. Using machine learning (gradient bousting and neural networks), with training on simulation data to predict tumor μ_a and μ_s based on light dose measurements using cylindrical diffusers, it is possible to optimize emitter location and power distribution by pre-planning based on average tissue optical properties. The light dose is also measured in real time using receiving optical fibers, the actual μ_a and μ_s are reconstructed using machine learning techniques, and then the power of the emitters is recalculated to minimize errors in the delivered dose magnitude. The methodology has been validated on 3D glioblastoma models. Results indicate that optical property restoration followed by power reoptimization reduces the uncertainty in dose prediction by 75% for healthy tissues. The method enhances treatment personalization by adapting to tissue changes during therapy, which may improve clinical outcomes in deep-seated tumors such as glioblastoma.

Conclusion

This review has considered the actual works devoted to the task of automation of planning and control of photodynamic therapy of gastrointestinal organs and highlighted several main directions for solving this task. First of all, automation is realized due to more effective calculation of the absorbed dose of therapeutic radiation using algorithms of numerical modeling of light propagation in tissues, information about the geometry of pathological inclusions and optical properties of normal and tumor tissues, determination of which is possible both at the preoperative stage and during the exposure itself. Two other important aspects of PDT planning and control are the control of photosensitizer photobleaching and oxygen concentration in the treatment zone, because without these components it is impossible for the photodynamic reaction to proceed according to type II. The methods of machine learning and artificial intelligence, which are currently primarily associated with automation of various processes, are just coming to the field of photodynamic treatment planning, as they require a sufficiently large amount of unified data for training classification models. However, their use already makes it possible to increase the accuracy and efficiency of determining the optical properties of tissues in order to optimize the location of emitters and the distribution of absorbed dose in the tissue volume by means of preliminary planning. Thus, we can conclude that automation of photodynamic treatment planning includes a number of important components, both algorithmic and technical, and represents an actively developing area of scientific research.

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