ISSN 2413-9432

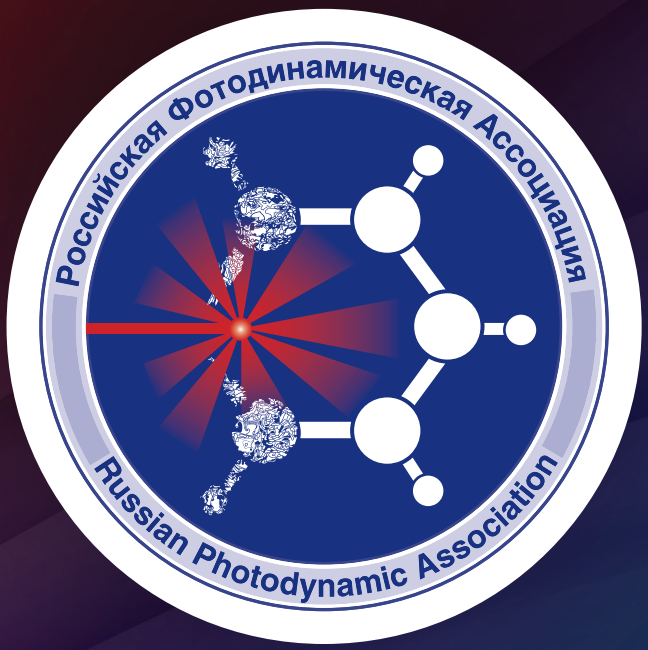
BIOMEDICAL PHOTONICS

Volume 12, # 4, 2023

In the issue:

BMP

Российская Фотодинамическая Ассоциация



www.pdt-association.com

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

Editorial staff:

Chief of the editorial staff	Ivanova-Radkevich V.I.
Science editor professor	Mamontov A.S.
Literary editor	Moiseeva R.N.
Translators	Kalyagina N.A.
Computer design	Kreneva E.I.
Desktop publishing	Shalimova N.M.

The Address of Editorial Office:
Russia, Moscow, 2nd Botkinskiy proezd, 3
Tel. 8 (495) 945–86–60
www: PDT-journal.com
E-mail: PDT-journal@mail.ru

Corresponding to:
125284, Moscow, p/o box 13

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

Редакция:

Зав. редакцией	Иванова-Радкевич В.И.
Научный редактор	проф. Мамонтов А.С.
Литературный редактор	Моисеева Р.Н.
Переводчики	Калягина Н.А.
Компьютерный дизайн	Кренева Е.И.
Компьютерная верстка	Шалимова Н.М.

Адрес редакции:
Россия, Москва, 2-й Боткинский пр., д. 3
Тел. 8 (495) 945–86–60
www: PDT-journal.com
E-mail: PDT-journal@mail.ru

Адрес для корреспонденции:
125284, Москва, а/я 13

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

ORIGINAL ARTICLES

ОРИГИНАЛЬНЫЕ СТАТЬИ

REVIEWS OF LITERATURE

ОБЗОРЫ ЛИТЕРАТУРЫ

CASE REPORTS

КЛИНИЧЕСКИЕ НАБЛЮДЕНИЯ

ORIGINAL ARTICLES

MODERN DIAGNOSTIC TECHNOLOGIES IN ONCODERMATOLOGY

Filonenko E.V., Kaprin A.D.
P.A. Herzen Moscow Oncology Research Center – branch of FSBI NMRRC of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract

Skin tumors occupy the first place in terms of incidence in the structure of oncological neoplasms. The WHO estimates that 60,000 people die each year from malignant neoplasms of the skin: 48,000 from melanoma and 12,000 from skin cancer. Timely diagnosis of skin cancer makes it possible to achieve a cure for cancer patients with long periods of relapse-free follow-up after the completion of specialized treatment. The introduction of high-tech optical methods for diagnosing skin neoplasms into clinical practice has significantly increased the specificity, sensitivity, and accuracy of diagnostics. The review is devoted to a discussion of such methods for diagnosing skin neoplasms as fluorescent diagnostics, digital dermatoscopy, SIA-scopy, and confocal microscopy. The features of the application of each of the methods are discussed, the results of the most significant Russian and foreign studies in this field are presented, as well as our own results of the practical application of a number of high-tech optical diagnostic methods at the P.A. Herzen Moscow Oncology Research Center.

Keywords: fluorescent diagnostics, digital dermatoscopy, SIA-scopy, confocal microscopy, melanoma, skin cancer.

Contacts: Filonenko E.V., e-mail: elena.filonenko@list.ru

For citations: Filonenko E.V., Kaprin A.D. Modern diagnostic technologies in oncodermatology, *Biomedical Photonics*, 2023, vol. 12, no. 4, pp. 4–14. doi: 10.24931/2413–9432–2023–12-4-4–14.

СОВРЕМЕННЫЕ ТЕХНОЛОГИИ ДИАГНОСТИКИ В ОНКОДЕРМАТОЛОГИИ

Е.В. Филоненко, А.Д. Каприн
«Московский научно-исследовательский онкологический институт им. П.А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации, Москва, Россия

Резюме

Опухоли кожи занимают первое место по заболеваемости в структуре онкологических новообразований. По оценкам ВОЗ, ежегодно от злокачественных новообразований кожи (ЗНО) умирает 60 000 человек: 48 000 с диагнозом меланома и 12 000 – рак кожи. Своевременная диагностика ЗНО кожи позволяет достигать излечения онкологических больных с длительными сроками безрецидивного наблюдения после завершения специализированного лечения. Внедрение в клиническую практику высокотехнологичных оптических методов диагностики новообразований кожи позволило значительно повысить специфичность, чувствительность и точность диагностики. Обзор посвящен обсуждению таких методов диагностики новообразований кожи, как флуоресцентная диагностика, цифровая дерматоскопия, СИА-скопия, конфокальная микроскопия. Обсуждены особенности применения каждого из методов, приведены результаты наиболее значимых российских и зарубежных исследований в данной области, а также собственные результаты практического применения высокотехнологичных методов диагностики в МНИОИ им. П.А. Герцена.

Ключевые слова: флуоресцентная диагностика, цифровая дерматоскопия, СИА-скопия, конфокальная микроскопия, меланома, рак кожи.

Контакты: Филоненко Е.В., e-mail: elena.filonenko@list.ru

Для цитирования: Филоненко Е.В., Каприн А.Д. Современные технологии диагностики в онкодерматологии // Biomedical Photonics. – 2023. – Т. 12, № 4. – С. 4–14. doi: 10.24931/2413–9432–2023–12-4-4–14.

Introduction

Skin tumors occupy first place among oncological neoplasms: in 2021 in Russia, the share of malignant skin tumors (except melanoma) was 11.8%, the share of melanoma was 2.0%. The incidence of skin cancer and melanoma has increased significantly over the past few decades. Thus, in 2011, 65,675 newly diagnosed cases of malignant skin tumors (except melanoma) and 8,718 newly diagnosed cases of melanoma were registered in Russia. In 2021, these numbers were 68,459 (10-year increase 4.2%) and 11,412 (10-year increase 30.9%), respectively [1]. Globally, 2 to 3 million cases of skin cancer and 132,000 cases of skin melanoma are diagnosed annually. The World Health Organization estimates that 60,000 people die each year due to prolonged sun exposure: 48,000 from melanoma and 12,000 from skin cancer [2].

For any localization of malignant neoplasms (MN), early diagnosis provides opportunities for cure or achieving long survival periods. If skin cancer is suspected, the first specialist to whom patients turn is a dermatologist, or less often an oncologist-dermatologist. Skin examination begins with a clinical examination. In clinical practice, three main algorithms for the clinical diagnosis of pigmented skin tumors are used: the ABCD rule, the 7-point Glasgow system, and the Fitzpatrick scale. The "ABCD" rule for diagnosing skin tumors was proposed in 1985 by R. Friedman [3,4]. It includes the assessment of pigmented skin tumors using 4 parameters: A – asymmetry of the pigment spot; B – border roughness; C – uneven coloring; D – diameter more than 6 mm. The presence of 3 or more signs indicates a malignant tumor. Since 1999, the ABCD rule has additionally introduced parameter E, intended for repeated dynamic monitoring of individuals at risk. Parameter E evaluates the dynamics of changes in color, shape and size of pigmented skin formations. The Fitzpatrick scale [4] includes six signs characteristic for melanoma: shape – rising above the skin level; change in size, acceleration of growth; the borders are irregular, the edges are jagged; asymmetry – one half of the tumor is different from the other; the size is large – the diameter of the tumor usually exceeds 5 mm; coloring is uneven. The Glasgow 7-point system [4], developed by researchers from the University of Glasgow (Scotland) in 1989, includes an assessment of seven signs of a neoplasm by which it can be characterized as malignant, three of which are basic, 4 are additional.

Timely diagnosis of malignant skin tumors with assessment of the exact boundaries and spread of tumor lesions across the skin allows for specialized treatment of patients that is adequate in scope. The primary diagnosis of skin tumors is based on the clinical picture obtained during a visual external examination of the patient. To confirm the diagnosis, various instrumental methods are used. The use of high-tech optical techniques significantly increases the sensitivity and specificity of diagnosis in patients with malignant skin tumors.

Diagnosis of skin tumors using optical instruments

The history of the use of optical instruments for diagnostics goes back more than 300 years. In 1663 J. Ch. Kolhaus was the first to use a microscope to study the blood vessels of the nail bed. In 1879, S. Hueter used a microscope to study in detail the blood capillaries of the lower lip. The next stage in the development of diagnostic microscopy was the creation of stationary models of monocular and binocular microscopes for skin capillaroscopy according to the drawings of O. Muller (1916-1920). In 1920, the results of research work on the diagnostic use of a binocular microdermatoscope were published, and the first hand-held monocular dermatoscope appeared in 1989 [5,6].

Dermatoscopy is still the gold standard for the primary diagnosis of skin neoplasms. The method is widely used, which in most cases allows patients to be timely referred for surgical treatment. However, the effectiveness of the technique depends on the experience of the dermatologist and, in some cases, does not allow correctly recognizing the lesion and making an accurate diagnosis [2]. The most accurate diagnostic method remains a biopsy with histological examination of the biopsy material. However, the widespread use of biopsy to diagnose all suspicious tumors is limited by the complexity and cost of the procedure. The use of optical diagnostic methods makes it possible in many cases to avoid performing unnecessary biopsies and to assess with high accuracy, quickly and simply the presence of signs of a malignant nature of the formation under study [2].

High-tech optical methods for diagnosing skin tumors

Currently, among modern highly effective technologies for diagnosing skin cancer, fluorescence diagnostics, digital dermatoscopy, SIA-scopy, and confocal microscopy are distinguished.

Fluorescence diagnosis (FD) makes it possible to identify non-melanocytic skin tumors and clarify the boundaries of tumor lesions by specific fluorescence that appears in tumor cells after the use of a special compound – a photosensitizer.

Digital dermatoscopy allows automatic mapping of the patient's body, creating a series of photographs that are then analyzed by artificial intelligence (AI).

Spectrophotometry (SIA-scopy) is a non-invasive method for examining the skin, helping to carry out differential diagnosis of melanocytic skin neoplasms.

Confocal microscopy is a type of light optical microscopy with increased optical resolution and microphoto contrast.

Fluorescence diagnostics

FD is a method for diagnosing non-melanocytic skin tumors, which makes it possible to identify clinically undetectable foci of skin cancer and clarify the boundaries of the spread of the tumor process. For fluorescence diagnosis, drugs based on 5-aminolevulinic acid (5-ALA) and its esters are most often used [7]. The high specificity and sensitivity of FD in relation to tumor and pretumor pathology of the skin, its clarity, ease of examination and interpretation of results have been confirmed by numerous studies (Table 1).

As can be seen from the data presented in Table. 1, FD has high specificity and sensitivity for many tumors: BCC, squamous cell skin cancer, actinic keratosis, extramammary Paget's cancer, etc. Most often, drugs based on 5-ALA and its esters are used for FD of skin tumors.

In the P.A. Herzen Moscow Oncology Research Center an FD method with 5-ALA in patients with skin cancer of various locations was developed, including visual assessment of fluorescence and local fluorescence spectroscopy. The distribution of 5-ALA-induced protoporphyrin IX after oral administration of the drug was studied by local fluorescence spectroscopy; The values of spectral-fluorescence diagnostic parameters characterizing foci of cancer and benign skin tumors were determined. Using the developed medical technologies, 237 skin cancer patients were examined (507 lesions). FD allowed to clarify the boundaries of tumor skin lesions in 100% of cases, which influenced the choice of resection boundaries during surgical treatment or the planning of radiation fields during PDT. In 64 (27.0%) of 237 patients, occult foci of skin cancer were diagnosed. The sensitivity of the method was 100%, specificity 61.5%, diagnostic accuracy 67.8%. Adverse reactions (skin phototoxicity) were noted in only 1 (0.04%) patient.

Conducted at P.A. Herzen Moscow Oncology Research Center research has shown that FD with 5-ALA is an effective method for clarifying the boundaries of skin cancer when planning specialized antitumor treatment. This method makes it possible to effectively identify hidden foci of cancer, especially in the group of patients with multiple tumor lesions of the skin against the background of multiple focal lesions of an unspecified morphological structure, and at the same time it is a safe research method (Fig. 1). FD with 5-ALA is indicated for patients before specialized antitumor treatment, mainly in the group of patients with head and neck skin cancer and patients with multiple tumor lesions.

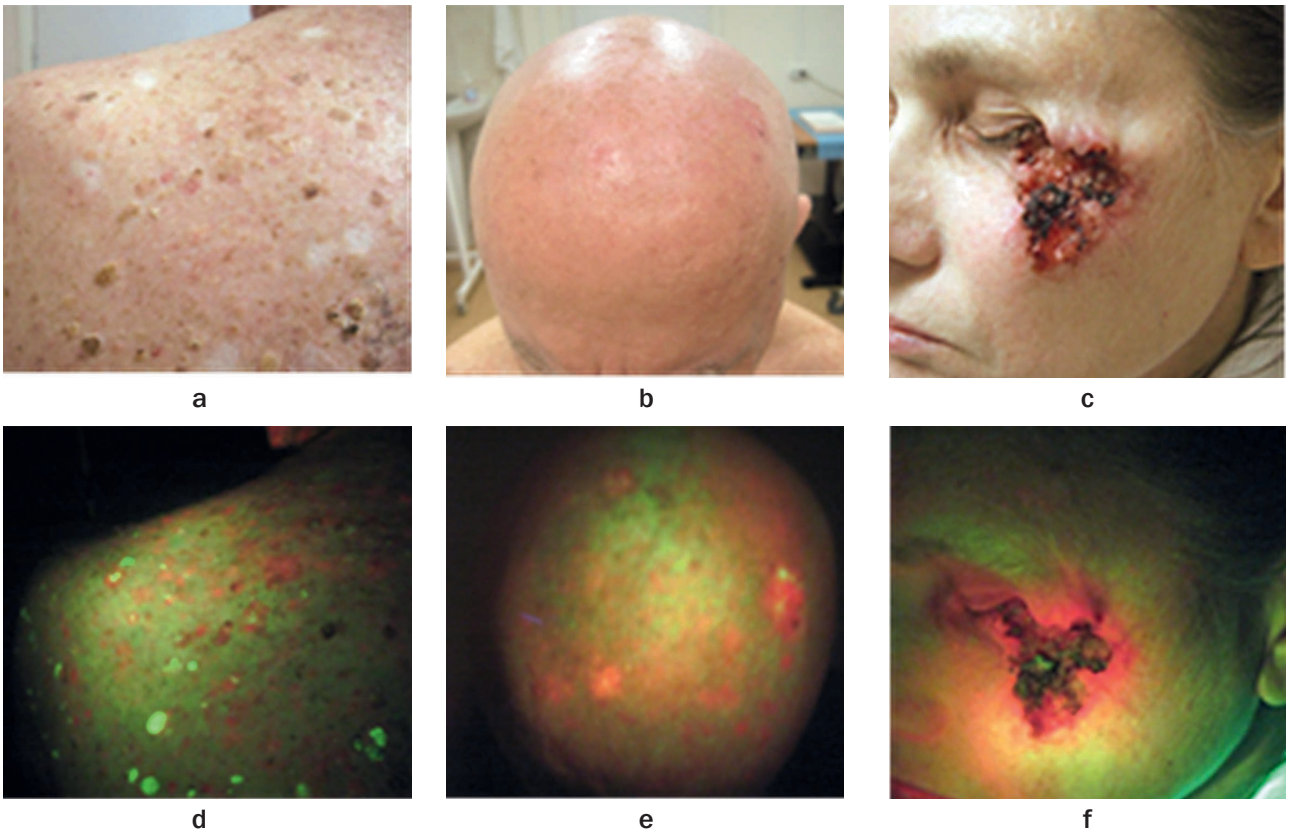


Рис. 1. Осмотр больных раком кожи в белом свете (a – пациент Б., 60 лет; b – пациент Э., 71 год; c – пациент П., 64 года) и в режиме флуоресценции (d – пациент Б., 60 лет; e – пациент Э., 71 год; f – пациент П., 64 года).
Fig. 1. Examination of patients with skin cancer in white light (a – patient B., 60 years old; b – patient E., 71 years old; c – patient P., 64 years old) and in fluorescence mode (d – patient B., 60 years old; e – patient E., 71 years old; f – patient P., 64 years old).

Таблица 1
Эффективность флуоресцентной диагностики у пациентов с немеланоцитарными опухолями кожи
Table 1
Efficiency of fluorescence diagnostics in patients with non-melanocytic skin tumors

	Авторы Authors	Число пациентов Number of Patients	Диагноз Diagnosis	Фотосенсибилизатор Photosensitizer	Результаты Results
1	Won et al., 2007 [8]	10	БКРК BCC	МЭ-АЛК 20% мазь MAL 20% ointment	Чувствительность – 82,6% Специфичность – 94,1% Sensitivity – 82.6% Specificity – 94.1%
2	Smits et al., 2007 [9]	14	86 очагов, в том числе 3 ПКРК, 67 актинический кератоз (32 KIN I, 18 KIN II, 17 KIN III), 10 нормальная кожа 86 lesions, including 3 SCC, 67 actinic keratosis (32 KIN I, 18 KIN II, 17 KIN III), 10 normal skin	5-АЛК 20% мазь 5-ALA 20% ointment	В исследовании показано отсутствие значимой разницы в показателях интенсивности флуоресценции между различными стадиями актинического кератоза. У большинства пациентов с болезнью Боуэна флуоресцентная контрастность была выше, чем у пациентов с актиническим кератозом в стадиях KIN I и KIN I The study shows no significant difference in fluorescence intensity between different stages of actinic keratosis. Most patients with Bowen's disease had higher fluorescence contrast than patients with actinic keratosis in stages KIN I and KIN I
3	Neus et al., 2008 [10]	28	БКРК BCC	5-АЛК 20% мазь 5-ALA 20% ointment	Чувствительность – 79% Специфичность – 100% Sensitivity – 79% Specificity – 100%
4	Van der Beek et al., 2012 [11]	30	БКРК Актинический кератоз BCC Actinic keratosis	5-АЛК 5-ALA	Показано преимущество использования для диагностики нормированной флуоресценции по сравнению с ненормированной флуоресценцией: специфичность и чувствительность при оценке нормированной флуоресценции составили 100% и 97% по сравнению с 27% и 39% The advantage of normalized fluorescence for diagnosis compared to non-normalized fluorescence is shown: specificity and sensitivity when assessing normalized fluorescence are 100% and 97% compared to 27% and 39%, respectively
5	Andrade et al., 2014 [12]	43	54 очагов (21 БКРК, 22 актинический кератоз, 11 себорейный кератоз) 54 lesions (21 BCC, 22 actinic keratosis, 11 seborrheic keratosis)	5-АЛК 5% раствор 5-ALA 5% solution	В очагах БКРК отмечено достоверное увеличение интенсивности флуоресценции в 3 раза через 1 час после нанесения раствора 5-АЛК. В очагах актинического и себорейного кератоза интенсивность флуоресценции в течение 1 ч после нанесения раствора 5-АЛК оставалась на уровне аутофлуоресценции In the lesions of BCC, a significant increase in fluorescence intensity by 3 times is noted 1 hour after application of the 5-ALA solution. In the foci of actinic and seborrheic keratosis, the fluorescence intensity remains at the autofluorescence level for 1 hour after application of the 5-ALA solution
6	Filonenko et al., 2015 [13]	227	БКРК, ПКРК, метатипический рак кожи BCC, SCC, metatypical skin cancer	5-АЛК 20% раствор для приема внутрь 5-ALA 20% oral solution	Чувствительность – 100,0% Специфичность – 55,6% Sensitivity – 100.0% Specificity – 55.6%
7	Wu et al., 2021 [14]	36	ВМРП EMPC	5-АЛК 20% раствор 5-ALA 20% solution	Визуальный осмотр – 63,8% ложноотрицательных результатов, ФД – 35,4% ложноотрицательных результатов, ФД + конфокальная микроскопия – 20,8% ложноотрицательных результатов By visual examination – 63.8% false negative results, FD – 35.4% false negative results, FD + confocal microscopy – 20.8% false negative results

МЭ-АЛК – метиловый эфир 5-аминолевулиновой кислоты, БКРК – базальноклеточный рак кожи, ПКРК – плоскоклеточный рак кожи, ВМРП – внемаммарный рак Педжета
MAL – methyl ester of 5-aminolevulinic acid, BCC – basal cell carcinoma, SCC – squamous cell carcinoma, EMPC – extramammary Paget's cancer

Digital dermatoscopy

Dermatoscopy using AI allows for photographic recording with an expert assessment of the condition of dermoscopic structures. AI based on a convolutional neural network is actively used in modern medicine for image recognition. In dermato-oncology, ultra-precise deep learning neural networks are used to recognize images obtained using a digital dermatoscope [15]. Numerous studies demonstrate the high effectiveness of digital dermatoscopy (Table 2).

The sensitivity and specificity of digital dermatoscopy varies significantly, as can be seen from the Table. 2. The sensitivity of the method is quite high regardless of the device used: up to 97.1%. The specificity for skin melanoma with the Melafind® dermatoscope (USA) is generally significantly lower (5.4-9.9%) than for FotoFinder® (Germany) (76.7-95.3%).

The authors [21], who used MelaFind, explain these results of the specificity of the method by the fact that it is intended for use in lesions with 1 or more clinical signs of melanoma, i.e. for any atypical lesions. If all atypical lesions were biopsied to rule out melanoma, the biopsy yield ratio (the number of false-positive biopsies per true-positive study) of approximately 200:1 would be very high. In a study [21], the biopsy ratio for MelaFind was 10.8:1 for melanomas and 7.6:1 for melanomas and borderline neoplasms. Moreover, the specificity of digital dermatoscopy with MelaFind exceeded the specificity of routine medical examination of patients in the same study (3.7%).

The authors also note that the rather low specificity of routine testing and MelaFind in this clinical trial does not mean that the specificity of clinician testing and MelaFind will be low in the general population. This is simply a reflection of the fact that almost all of the lesions in this study were atypical enough to be selected for biopsy to rule out malignant melanoma.

In P.A. Herzen Moscow Oncology Research Center a technique for digital dermatoscopy of skin tumors was introduced. We present two clinical examples demonstrating the effectiveness of this approach to the diagnosis of skin melanoma.

Clinical observation 1

Patient D., 66 years old, has been under observation for 5 years for breast cancer. During a follow-up

Таблица 2
Эффективность цифровой дерматоскопии меланомы кожи
Table 2
Effectiveness of digital dermatoscopy for skin melanoma

	Автор Authors	Количество образований Number of Neoplasmes	Используемый прибор Device	Результаты Results
1	MacLellan et al., 2020 [16]	209	FotoFinder® (Германия/Germany) Melafind® (США/USA) Verisante AuraTM (Канада/Canada)	Чувствительность и специфичность: MelaFind® 82,5% и 5,4%, соответственно Verisante Aura TM 21,4% и 86,2%, соответственно FotoFinder® 88,1% и 78,8%, соответственно Sensitivity and specificity: MelaFind® 82.5% and 5.4%, respectively Verisante Aura TM 21.4% and 86.2%, respectively FotoFinder® 88.1% and 78.8%, respectively
2	Sies et al., 2020 [17]	1981	FotoFinder® (Германия/Germany)	Чувствительность – 77,6% Специфичность – 95,3% Sensitivity – 77.6% Specificity – 95.3%
3	Fink et al., 2020 [18]	72	FotoFinder® (Германия/Germany)	Чувствительность – 97,1% Специфичность – 78,8% Sensitivity – 97.1% Specificity – 78.8%
4	Fujisawa et al., 2019 [19]	1142	GoogLeNet DCNN model	Чувствительность – 96,3% Специфичность – 89,5% Sensitivity – 96.3% Specificity – 89.5%
5	Haenssle et al., 2019 [20]	100	FotoFinder® (Германия/Germany)	Чувствительность – 95% Специфичность – 76,7% Sensitivity – 95% Specificity – 76.7%
6	Monheit et al.,2011 [21]	1632	Melafind® (США/USA)	Чувствительность – 95,6% Специфичность – 9,9% Sensitivity – 95.6% Specificity – 9.9%

examination, the oncologist identified a suspicious pigmented formation on the skin of the right cheek. According to the patient, the formation has been noted for a long time and has no complaints. The patient underwent digital dermatoscopy (Fig. 2). Automatic AI score – 0.88. According to the histological report performed after an excisional biopsy, epithelial pigment cell, nonulcerated lentigo melanoma *in situ* with moderate subepithelial lymphoid plasma cell infiltration was diagnosed (Fig. 3). The patient was diagnosed with stage 0 melanoma pTisN0M0 of the skin of the right cheek.

Clinical observation 2

Patient V., 60 years old, noted the presence of a pigmented formation on the skin of the back for a long time. Over the past three weeks noticed a change in the color of the neoplasm and felt discomfort in the area of the tumor, thus independently consulted an oncologist. The patient underwent digital dermatoscopy (Fig. 4). Automatic AI assessment – 0.9-1.0. According to the histological conclusion a superficial spreading pigment epithelial cell melanoma in the horizontal growth phase was revealed, Clark level II invasion, Breslow thickness less than 0.5 mm, resection margins intact (Fig. 5). The patient was diagnosed with IA stage pT1aN0M0 skin melanoma of the back.

Spectrophotometry (SIA-scopy)

SIA-scopy is a method for diagnosing skin tumors, which is based on the analysis of a spectrophotometric intradermal image. SIA-scopy allows to assess the state of dermal collagen, the severity of blood flow in the papillary layer of the dermis, and diagnose the level of localization of dermal and epidermal melanin [22]. The use of SIA-scopy demonstrates high sensitivity and specificity for skin tumors (Table 3).

As can be seen from the Table. 3, the sensitivity of SIA-scopy ranges from 66.6-100%. Only one study obtained abnormally low results for assessing the sensitivity of the technique – 24% [27]. The authors concluded that diagnosis based on SIA-scopy has low diagnostic accuracy for melanoma, individual signs of SIA-scopy do not provide reliable diagnostic information regarding the internal structure of lesions during histopathological examination, and SIA-scopy cannot be used as a guide

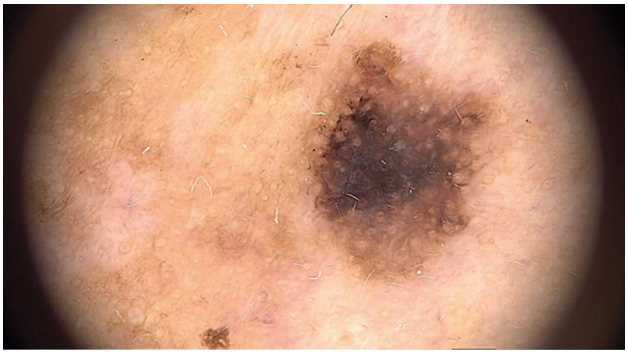


Рис. 2. Результаты цифровой дерматокскопии меланомы кожи правой щеки (FotoFinder®, Германия).
Fig. 2. Results of digital dermatoscopy of melanoma of the skin of the right cheek (FotoFinder®, Germany).

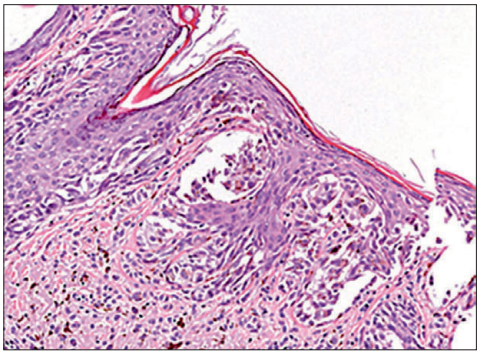


Рис. 3. Гистологическое исследование меланомы кожи правой щеки.
Fig. 3. Histological examination of melanoma of the skin of the right cheek.

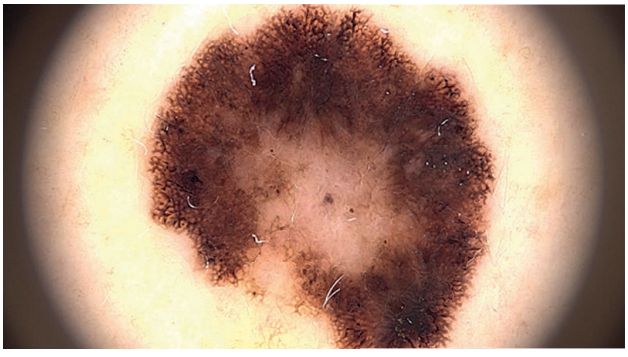


Рис. 4. Результаты цифровой дерматокскопии меланомы кожи спины (FotoFinder®, Германия).
Fig. 4. Results of digital dermatoscopy of melanoma of the skin of the back (FotoFinder®, Germany).

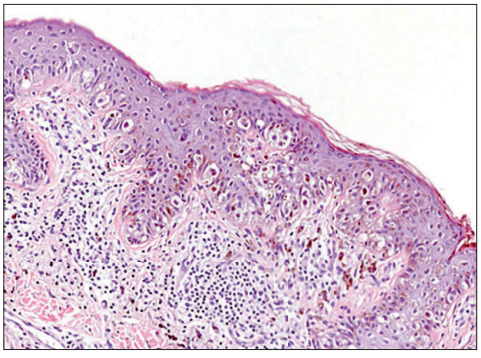


Рис. 5. Гистологическое исследование меланомы кожи спины.
Fig. 5. Histological examination of melanoma of the skin of the back.

Таблица 3
Эффективность СИА-скопии
Table 3
Efficiency of SIA-scopy

	Автор Authors	Количество образований Number of Neoplasmes	Используемый прибор Device	Результаты Results
1	Moncrieff et al., 2002 [22]	348 пигментированных образований кожи (включая 52 меланомы) 348 pigmented skin lesions (including 52 melanomas)	SIAscope (Великобритания Great Britain)	Чувствительность – 82,7% Специфичность – 80,1% Sensitivity – 82.7% Specificity – 80.1%
2	Haniffa et al., 2007 [23]	881 пигментное образование (включая 31 меланому) 881 pigmented lesions (including 31 melanomas)	1. Дерматоскоп 2. SIAscope (Великобритания/ Great Britain)	Добавление СИА-скопии не изменило показатели чувствительности и специфичности дерматоскопии – 94% и 91%, соответственно The addition of SIA-scopy did not change the sensitivity and specificity of dermatoscopy – 94% and 91%, respectively
3	Carrara et al., 2007 [24]	1966 (287 меланом) 1966 (287 melanomas)	SIAscope (Великобритания/ Great Britain)	Чувствительность – 88% Специфичность – 80,0% Sensitivity – 88% Specificity – 80.0%
4	Ascierto et al., 2010 [25]	54	Spectroshade® (Италия/Italy)	Чувствительность – 66,6% Специфичность – 76,2% Sensitivity – 66.6% Specificity – 76.2%
5	Glud et al., 2009 [26]	83	SIAscope (Великобритания/ Great Britain)	Чувствительность – 100% Специфичность – 59% Sensitivity – 100% Specificity – 59%
6	Terstappen et al., 2013 [27]	60 (42 меланомы, включая 13 in situ) 60 (42 melanomas, including 13 in situ)	SIAscope (Великобритания/ Great Britain)	Чувствительность – 24% Специфичность – 84% Sensitivity – 24% Specificity – 84%
7	Sgouros et al., 2014 [28]	188 (18 меланом) 188 (18 melanomas)	SIAscope (Великобритания/ Great Britain)	Чувствительность – 85,7% Специфичность – 65,4% Sensitivity – 85.7% Specificity – 65.4%

to determine the maximum tumor thickness during histopathological examination.

In all other studies, the authors emphasize the high diagnostic value of SIA-scopy. Probably, an important role in the correct interpretation of the results of SIA-scopy is played by the proven methodology and algorithms for evaluating SIA-scans. Therefore, at the P.A. Herzen Moscow Oncology Research Center a work that made it possible to develop the semiotics of SIA-scopic images was carried out, which significantly increased the efficiency of using this method.

Using a developed SIA-scopy algorithm 327 pigmented skin formations in 147 patients were analyzed. The study results were assessed by comparing data from spectrophotometric analysis with data from routine histological examination of 327 lesions. The semiotics of the spectrophotometric image was determined and a working classification for assessing the spectrophotometric image for 2, 3, 4, 5 SIA scans was developed.

Significant criteria for the malignancy of pigmented neoplasms were determined using the spectrophotometric analysis technique, which made it possible to non-invasively diagnose skin melanoma with sensitivity – 96%, specificity – 100%, and diagnostic accuracy – 99%. The most informative SIA scans in the non-invasive diagnosis of melanoma have been identified, characterizing the amount of melanin in the papillary layer of the dermis, and the state of blood vessels and collagen fibers: SIA scans 3, 4, 5 (Fig. 6).

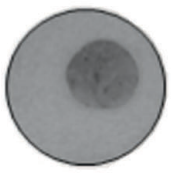
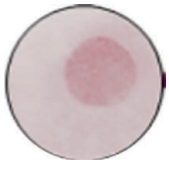
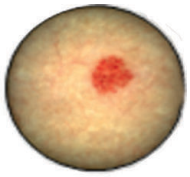
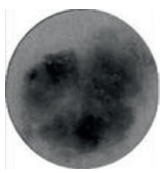
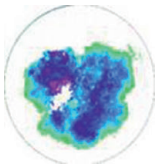
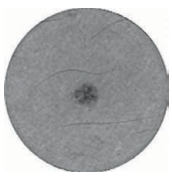
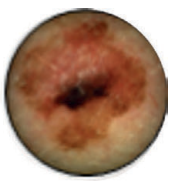
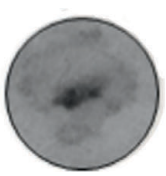
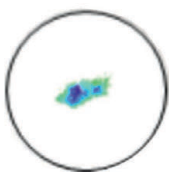
Диагноз Diagnostic	СИА-скопические изображения SIA-scopic images				
	СИА-1 SIA-1	СИА-2 SIA-2	СИА-3 SIA-3	СИА-4 SIA-4	СИА-5 SIA-5
Кератома Keratoma					
Гемангиома Hemangioma					
Меланома Melanoma					
Невус Nevus					
Меланома in situ Melanoma in situ					

Рис. 6. СИАскопические изображения.
Fig. 6. SIAscopic images.

Confocal microscopy

Confocal microscopy (confocal laser scanning microscopy) is a type of optical light microscopy. It allows to increase the optical resolution and contrast of a microphotography by using a pinhole diaphragm to block out-of-focus light or glare during image formation. The advantages of confocal microscopy also include the ability to obtain a series of sequential optical sections from thick samples, the thickness of which exceeds the immediate plane of focus, and then reconstruct a three-dimensional image of the sample from these series [29,30].

Confocal microscopy is carried out in two modes: reflective (the highest signal intensity usually occurs during the transition between air and the surface of the sample; more suitable for visualizing the topography of surfaces) and fluorescent (allows to visualize not only the general structure of the skin, but also individual target molecules in skin cells) [29].

A number of studies demonstrate the high efficiency of using both modes of confocal microscopy in clinical practice for the diagnosis of skin tumors (Table 4).

Confocal microscopy shows sensitivity and specificity comparable to other high-tech optical methods for diagnosing skin tumors, up to 100% and 95%, respectively. At the same time, the specificity for pigmented melanoma was slightly lower than for other neoplasms – 65%.

Conclusion

Thus, the diagnosis of skin tumors with high-tech optical techniques allows for primary and clarifying

Таблица 4
Эффективность конфокальной микроскопии
Table 4
The efficiency of confocal microscopy

	Автор Author	Количество образований Number of formations	Режим Mode	Результаты Results
1	Guitera et al., 2009 [30]	Меланома, невус >300 Melanoma, nevus >300	Отражательная конфокальная микроскопия Reflectance confocal microscopy	Пигментированная меланома: Специфичность – 65% Чувствительность – 92% Беспигментная меланома Специфичность – 84% Чувствительность – 85% Pigmented melanoma: Specificity – 65% Sensitivity – 92% Amelanotic melanoma Specificity – 84% Sensitivity – 85%
2	Guitera et al., 2012 [31]	Меланома, БКРК, невус, пигментированные пятна на лице, другие опухоли >700 Melanoma, BCC, nevus, pigmented spot on face, others tumors >700	Отражательная конфокальная микроскопия Reflectance confocal microscopy	Специфичность – 88,5% Чувствительность – 100% Specificity – 88.5% Sensitivity – 100%
3	Segura et al., 2012 [32]	Меланома, БКРК, ПКРК, кератоз, невус >150 Melanoma, BCC, SCCC, keratosis, nevus >150	Отражательная конфокальная микроскопия Reflectance confocal microscopy	Специфичность – 95,3% Чувствительность – 86,1% Specificity – 95.3% Sensitivity – 86.1%
4	Horn et al., 2008 [33]	Актинический кератоз, здоровая кожа с высоким риском развития новообразований 30 Actinic keratosis, healthy skin with a high risk of developing tumors 30	Отражательная конфокальная микроскопия Reflectance confocal microscopy	Специфичность – 88,3% Чувствительность – 93,3% Specificity – 88.3% Sensitivity – 93.3%
5	Gareau et al., 2009 [34]	БКРК, здоровая кожа >40 BKRK, healthy skin >40	Флуоресцентная конфокальная микроскопия Fluorescence confocal microscopy	Специфичность – 89,2% Чувствительность – 96,6% Specificity – 89.2% Sensitivity – 96.6%

diagnosis of skin cancer with high efficiency. Depending on the medical technology used, it is possible to perform early diagnosis of latent foci of malignant neoplasms of melanocytic and non-melanocytic nature, assess the extent and boundaries of the tumor along the surface of the skin in non-melanocytic tumors, as well as remote consultation of clinical observations using telemedicine technologies.

REFERENCES

1. Sostoyanie onkologicheskoi pomoshchi naseleniyu v Rossii v 2021 godu. Ed by Kaprin A.D., Starinskii V.V., Shakhzadova A.O. Moscow: MNIOI im. P.A. Gertsena – filial FGBU «FMITs im. P.A Gertsena» Minzdrava Rossii; 2022. (In Russ).
2. Rey-Barroso L., Peña-Gutiérrez S., Yáñez C., et al. Optical Technologies for the Improvement of Skin Cancer Diagnosis: A Review. *Sensors*, 2021, vol. 21(1), pp. 252. https://doi.org/10.3390/s21010252
3. Abbasi N.R., Shaw H.M., Rigel D.S., Friedman R.J. et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA*, 2004, vol. 292(22), pp. 2771-2776. https://doi.org/10.1001/jama.292.22.2771

ЛИТЕРАТУРА

1. *Состояние онкологической помощи населению в России в 2021 году* / Под ред. Каприна А.Д., Старинского В.В., Шахзадовой А.О. – М.: МНИОИ им. П.А. Герцена – филиал ФГБУ «ФМИЦ им. П.А Герцена» Минздрава России. – 2022.
2. Rey-Barroso L., Peña-Gutiérrez S., Yáñez C., et al. Optical Technologies for the Improvement of Skin Cancer Diagnosis: A Review // *Sensors*. – 2021. – Vol. 21(1). – P. 252. https://doi.org/10.3390/s21010252
3. Abbasi N.R., Shaw H.M., Rigel D.S., Friedman R.J., et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria // JAMA. – 2004. – Vol. 292(22). – P. 2771-2776. https://doi.org/10.1001/jama.292.22.2771

4. Ufimtseva M.A., Petkau V.V., Shubina A.S., et al. Algoritmy rannei diagnostiki melanomy kozhi. *Lechashchii vrach*, 2016, vol. 12. (In Russ.)
5. Goldman L. Some investigative studies of pigmented nevi with cutaneous microscopy. *J Invest Dermatol*, 1951, vol. 16(6), pp. 407-427. doi:10.1038/jid.1951.48
6. Argenziano G., Fabbrocini G., Carli P., De Giorgi V., et al. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Arch Dermatol*, 1998, vol. 134(12), pp. 1563-1570. doi:10.1001/archderm.134.12.1563
7. Filonenko E, Ivanova-Radkevich V. Fluorescent diagnostics of non-melanoma skin cancer. *Biomedical Photonics,* 2022, vol. 11(4), pp. 32-40. https://doi.org/10.24931/2413-9432-2022-11-4-32-40
8. Won Y., Hong S.H., Yu H.Y., et al. Photodetection of basal cell carcinoma using methyl 5-aminolaevulinate-induced protoporphyrin IX based on fluorescence image analysis. *Clin Exp Dermatol.* 2007, vol. 32, pp. 423-429.
9. Smits T., Kleinpenning M.M., Blokx W.A., et al. Fluorescence diagnosis in keratinocytic intraepidermal neoplasias. *J Am Acad Dermatol*, 2007, vol. 57, pp. 824-831.
10. Neus S., Gambichler T., Bechara F.G., et al. Preoperative assessment of basal cell carcinoma using conventional fluorescence diagnosis. *Arch Dermatol Res*, 2009, vol. 301(4), pp. 289-294. doi: 10.1007/s00403-008-0911-9
11. Van der Beek N., Leeuw J., Demmendal C., et al. PpIX fluorescence combined with auto-fluorescence is more accurate than PpIX fluorescence alone in fluorescence detection of non-melanoma skin cancer: an intra-patient direct comparison study. *Laser Surg Med*, 2012, vol. 44, pp. 271-276.
12. Andrade C.T., Vollet-Filho J.D., Salvio A.G., et al. Identification of skin lesions through aminolaevulinic acid-mediated photodynamic detection. *Photodiagnosis Photodyn Ther*, 2014, vol. 11(3), pp. 409-415. doi: 10.1016/j.pdpdt.2014.05.006
13. Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy in the treatment of extramammary Paget's disease. *Biomedical Photonics*, 2022, vol. 11(3), pp. 4-34. https://doi.org/10.24931/2413-9432-2022-11-3-24-34
14. Wu M., Huang L., Lu X., et al. Utility of photodynamic diagnosis plus reflectance confocal microscopy in detecting the margins of extramammary Paget disease. *Indian J Dermatol Venereol Leprol*, 2021, vol. 87(2), pp. 207-213. doi: 10.25259/IJDVL_90_20
15. Zhang Z., Zhang K., Khelifi A. Multivariate time series analysis in climate and environmental research. *Cham: Springer International Publishing*, 2018.
16. MacLellan A.N., Price E.L., Publicover-Brouwer P., et al. The use of noninvasive imaging techniques in the diagnosis of melanoma: a prospective diagnostic accuracy study. *J Am Acad Dermatol*, 2021, vol. 85(2), pp. 353-359. doi:10.1016/j.jaad.2020.04.019
17. Sies K., Winkler J.K., Fink C., et al. Past and present of computer-assisted dermoscopic diagnosis: performance of a conventional image analyser versus a convolutional neural network in a prospective data set of 1,981 skin lesions. *Eur J Cancer*, 2020, vol. 135, pp. 39-46. doi:10.1016/j.ejca.2020.04.043
18. Fink C, Blum A, Buhl T, et al. Diagnostic performance of a deep learning convolutional neural network in the differentiation of combined naevi and melanomas. *J Eur Acad Dermatol Venereol,* 2020, vol. 34(6), pp. 1355-1361. doi:10.1111/jdv.16165
19. Fujisawa Y., Otomo Y., Ogata Y., et al. Deep-learning-based, computer-aided classifier developed with a small dataset of clinical images surpasses board-certified dermatologists in skin tumour diagnosis. *Br J Dermatol*, 2019, vol. 180(2), pp. 373-381. doi:10.1111/bjd.16924
20. Haenssle H.A., Fink C., Toberer F., et al. Man against machine reloaded: performance of a market-approved convolutional neural network in classifying a broad spectrum of skin lesions in comparison with 96 dermatologists working under less artificial conditions. *Ann Oncol*, 2020, vol. 31(1), pp. 137-143. doi:10.1016/j.annonc.2019.10.013

4. Уфимцева М.А., Петкау В.В., Шубина А.С. и др. Алгоритмы ранней диагностики меланомы кожи // Лечащий врач. – 2016. – № 12.
5. Goldman L. Some investigative studies of pigmented nevi with cutaneous microscopy // J Invest Dermatol. – 1951. – Vol. 16(6). – P. 407-427. doi:10.1038/jid.1951.48
6. Argenziano G., Fabbrocini G., Carli P., De Giorgi V., et al. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis // Arch Dermatol. – 1998. – Vol. 134(12). – P. 1563-1570. doi:10.1001/archderm.134.12.1563
7. Filonenko E., Ivanova-Radkevich V. Fluorescent diagnostics of non-melanoma skin cancer // Biomedical Photonics. – 2022. – Vol. 11(4). – P. 32-40. https://doi.org/10.24931/2413-9432-2022-11-4-32-40
8. Won Y., Hong S.H., Yu H.Y., et al. Photodetection of basal cell carcinoma using methyl 5-aminolaevulinate-induced protoporphyrin IX based on fluorescence image analysis // Clin Exp Dermatol. – 2007. – Vol. 32. – P. 423-429.
9. Smits T., Kleinpenning M.M., Blokx W.A., et al. Fluorescence diagnosis in keratinocytic intraepidermal neoplasias // J Am Acad Dermatol. – 2007. – Vol. 57. – P. 824-831.
10. Neus S., Gambichler T., Bechara F.G., et al. Preoperative assessment of basal cell carcinoma using conventional fluorescence diagnosis // Arch Dermatol Res. – 2009. – Vol. 301(4). – P. 289-294. doi: 10.1007/s00403-008-0911-9
11. Van der Beek N., Leeuw J., Demmendal C., et al. PpIX fluorescence combined with auto-fluorescence is more accurate than PpIX fluorescence alone in fluorescence detection of non-melanoma skin cancer: an intra-patient direct comparison study // Laser Surg Med. – 2012. – Vol. 44. – P. 271-276.
12. Andrade C.T., vollet-Filho J.D., Salvio A.G., et al. Identification of skin lesions through aminolaevulinic acid-mediated photodynamic detection // Photodiagnosis Photodyn Ther. – 2014. – Vol. 11(3). – P. 409-415. doi: 10.1016/j.pdpdt.2014.05.006
13. Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy in the treatment of extramammary Paget's disease // Biomedical Photonics. – 2022. – Vol. 11(3). – P. 4-34. https://doi.org/10.24931/2413-9432-2022-11-3-24-34
14. Wu M., Huang L., Lu X., et al. Utility of photodynamic diagnosis plus reflectance confocal microscopy in detecting the margins of extramammary Paget disease // Indian J Dermatol Venereol Leprol. – 2021. – Vol. 87(2). – P. 207-213. doi: 10.25259/IJDVL_90_20
15. Zhang Z., Zhang K., Khelifi A. Multivariate time series analysis in climate and environmental research // Cham: Springer International Publishing. – 2018.
16. MacLellan A.N., Price E.L., Publicover-Brouwer P., et al. The use of noninvasive imaging techniques in the diagnosis of melanoma: a prospective diagnostic accuracy study // J Am Acad Dermatol. – 2021. – Vol. 85(2). – P. 353-359. doi:10.1016/j.jaad.2020.04.019
17. Sies K., Winkler J.K., Fink C., et al. Past and present of computer-assisted dermoscopic diagnosis: performance of a conventional image analyser versus a convolutional neural network in a prospective data set of 1981 skin lesions // Eur J Cancer. – 2020. – Vol. 135. – P. 39-46. doi:10.1016/j.ejca.2020.04.043
18. Fink C., Blum A., Buhl T., et al. Diagnostic performance of a deep learning convolutional neural network in the differentiation of combined naevi and melanomas // J Eur Acad Dermatol Venereol. – 2020. – Vol. 34(6). – P. 1355-1361. doi:10.1111/jdv.16165
19. Fujisawa Y., Otomo Y., Ogata Y., et al. Deep-learning-based, computer-aided classifier developed with a small dataset of clinical images surpasses board-certified dermatologists in skin tumour diagnosis // Br J Dermatol. – 2019. – Vol. 180(2). – P. 373-381. doi:10.1111/bjd.16924
20. Haenssle H.A., Fink C., Toberer F., et al. Man against machine reloaded: performance of a market-approved convolutional neural network in classifying a broad spectrum of skin lesions in comparison with 96 dermatologists working under less artificial condi-

21. Monheit G., Cognetta A.B., Ferris L., et al. The performance of MelaFind: a prospective multicenter study. *Arch Dermatol*, 2011, vol. 147(2), pp. 188-194. doi:10.1001/archdermatol.2010.302
22. Moncrieff M, Cotton S, Claridge E, Hall P. Spectrophotometric intracutaneous analysis: a new technique for imaging pigmented skin lesions. Br J Dermatol. 2002;146(3):448-457. doi:10.1046/j.1365-2133.2002.04569.x
23. Haniffa M.A., Lloyd J.J., Lawrence C.M. The use of a spectrophotometric intracutaneous analysis device in the real-time diagnosis of melanoma in the setting of a melanoma screening clinic. *Br J Dermatol*, 2007, vol. 156(6), pp. 1350-1352. doi:10.1111/j.1365-2133.2007.07932.x
24. Carrara M., Bono A., Bartoli C., et al. Multispectral imaging and artificial neural network: mimicking the management decision of the clinician facing pigmented skin lesions. *Phys Med Biol*, 2007, vol. 52(9), pp. 2599-2613. doi:10.1088/0031-9155/52/9/018
25. Ascierto P.A., Palla M., Ayala F., et al. The role of spectrophotometry in the diagnosis of melanoma. *BMC Dermatol*, 2010, vol. 10, p. 5. doi:10.1186/1471-5945-10-5
26. Glud M., Gniadecki R., Drzewiecki K.T. Spectrophotometric intracutaneous analysis versus dermoscopy for the diagnosis of pigmented skin lesions: prospective, double-blind study in a secondary reference centre. *Melanoma Res*, 2009, vol. 19(3), pp. 176-179. doi:10.1097/CMR.0b013e328322fe5f
27. Terstappen K., Suurküla M., Hallberg H., et al. Poor correlation between spectrophotometric intracutaneous analysis and histopathology in melanoma and nonmelanoma lesions. *J Biomed Opt*, 2013, vol. 18(6), pp. 061223. doi:10.1117/1.JBO.18.6.061223
28. Sgouros D., Lallas A., Julian Y., et al. Assessment of SIAscopy in the triage of suspicious skin tumours. *Skin Res Technol*, 2014, vol. 20(4), pp. 440-444. doi:10.1111/srt.12138
29. Rey-Barroso L., Peña-Gutiérrez S., Yáñez C., Burgos-Fernández F.J., Vilaseca M., Royo S. Optical Technologies for the Improvement of Skin Cancer Diagnosis: A Review. *Sensors (Basel)*, 2021, vol. 21(1), p. 252. doi:10.3390/s21010252
30. Guitera P., Pellacani G., Longo C., et al. In Vivo Reflectance Confocal Microscopy Enhances Secondary Evaluation of Melanocytic Lesions. *J. Investig. Dermatol*, 2009, vol. 129, pp. 131-138. doi:10.1038/jid.2008.193.
31. Guitera P, Menzies SW, Longo C, et al. In Vivo Confocal Microscopy for Diagnosis of Melanoma and Basal Cell Carcinoma Using a Two-Step Method: Analysis of 710 Consecutive Clinically Equivocal Cases. *J. Investig. Dermatol*, 2012, vol. 132, pp. 2386-2394. doi:10.1038/jid.2012.172.
32. Segura S., Puig S., Carrera C., et al. Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy. *J. Am. Acad. Dermatol*, 2009, vol. 61, pp. 216-229. doi:10.1016/j.jaad.2009.02.014.
33. Horn M., Gerger A., Ahlgrimm-Siess V., et al. Discrimination of actinic keratoses from normal skin with reflectance mode confocal microscopy. *Dermatol. Surg*, 2008, vol. 34, pp. 620-625.
34. Gareau D.S., Li Y., Huang B., et al. Confocal mosaicing microscopy in Mohs skin excisions: Feasibility of rapid surgical pathology. *J. Biomed. Opt*, 2008, vol. 13, p. 054001. doi: 10.1117/1.2981828.

tions // Ann Oncol. – 2020. – Vol. 31(1). – P. 137-143. doi:10.1016/j.annonc.2019.10.013
21. Monheit G., Cognetta A.B., Ferris L., et al. The performance of MelaFind: a prospective multicenter study // Arch Dermatol. – 2011. – Vol. 147(2). – P. 188-194. doi:10.1001/archdermatol.2010.302
22. Moncrieff M., Cotton S., Claridge E., Hall P. Spectrophotometric intracutaneous analysis: a new technique for imaging pigmented skin lesions // Br J Dermatol. – 2002. – Vol. 146(3). – P. 448-457. doi:10.1046/j.1365-2133.2002.04569.x
23. Haniffa M.A., Lloyd J.J., Lawrence C.M. The use of a spectrophotometric intracutaneous analysis device in the real-time diagnosis of melanoma in the setting of a melanoma screening clinic // Br J Dermatol. – 2007. – Vol. 156(6). – P. 1350-1352. doi:10.1111/j.1365-2133.2007.07932.x
24. Carrara M., Bono A., Bartoli C., et al. Multispectral imaging and artificial neural network: mimicking the management decision of the clinician facing pigmented skin lesions // Phys Med Biol. – 2007. – Vol. 52(9). – P. 2599-2613. doi:10.1088/0031-9155/52/9/018
25. Ascierto P.A., Palla M., Ayala F., et al. The role of spectrophotometry in the diagnosis of melanoma // BMC Dermatol. – 2010. – Vol. 10. – P. 5. doi:10.1186/1471-5945-10-5
26. Glud M., Gniadecki R., Drzewiecki K.T. Spectrophotometric intracutaneous analysis versus dermoscopy for the diagnosis of pigmented skin lesions: prospective, double-blind study in a secondary reference centre // Melanoma Res. – 2009. – Vol. 19(3). – P. 176-179. doi:10.1097/CMR.0b013e328322fe5f
27. Terstappen K., Suurküla M., Hallberg H., et al. Poor correlation between spectrophotometric intracutaneous analysis and histopathology in melanoma and nonmelanoma lesions // J Biomed Opt. – 2013. – Vol. 18(6). – P. 061223. doi:10.1117/1.JBO.18.6.061223
28. Sgouros D., Lallas A., Julian Y., et al. Assessment of SI Ascopy in the triage of suspicious skin tumours // Skin Res Technol. – 2014. – Vol. 20(4). – P. 440-444. doi:10.1111/srt.12138
29. Rey-Barroso L., Peña-Gutiérrez S., Yáñez C., Burgos-Fernández F.J., Vilaseca M., Royo S. Optical Technologies for the Improvement of Skin Cancer Diagnosis: A Review // Sensors (Basel) . – 2021. – Vol. 21(1). – P. 252. doi:10.3390/s21010252
30. Guitera P., Pellacani G., Longo C., et al. In Vivo Reflectance Confocal Microscopy Enhances Secondary Evaluation of Melanocytic Lesions // J. Investig. Dermatol. – 2009. – Vol. 129. – P. 131-138. doi: 10.1038/jid.2008.193.
31. Guitera P., Menzies S.W., Longo C., et al. In Vivo Confocal Microscopy for Diagnosis of Melanoma and Basal Cell Carcinoma Using a Two-Step Method: Analysis of 710 Consecutive Clinically Equivocal Cases // J. Investig. Dermatol. – 2012. – Vol. 132. – P. 2386-2394. doi: 10.1038/jid.2012.172.
32. Segura S., Puig S., Carrera C., et al. Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy // J. Am. Acad. Dermatol. – 2009. – Vol. 61. – P. 216-229. doi: 10.1016/j.jaad.2009.02.014.
33. Horn M., Gerger A., Ahlgrimm-Siess V., et al. Discrimination of actinic keratoses from normal skin with reflectance mode confocal microscopy // Dermatol. Surg. – 2008. – Vol. 34. – P. 620-625.
34. Gareau D.S., Li Y., Huang B., et al. Confocal mosaicing microscopy in Mohs skin excisions: Feasibility of rapid surgical pathology // J. Biomed. Opt. – 2008. – Vol. 13. – P. 054001. doi: 10.1117/1.2981828.

ANATOMICAL-FUNCTIONAL STATE OF SURFACE LYMPHATIC SYSTEM OF LOWER EXTREMITIES IN CHRONIC VEIN DISEASES ACCORDING TO FLUORESCENCE LYMPHOGRAPHY

Abduvosidov Kh.A.[1,2,3], Chudnykh S.M.[2,4], Shestakova V.G.[3], Alekseev A.G.[1], Kokoev M.M.[4], Kozlov N.S.[4], Korolyuk G.M.[4]
[1]Russian Biotechnology University, Moscow, Russia
[2]Loginov Moscow Clinical Scientific and Practical Center, DHM, Moscow, Russia
[3]Tver State Medical University, Tver, Russia
[4]Moscow State University of Medicine and Dentestry named after A.I. Evdokimov, Moscow, Russia

Abstract

Despite the large arsenal of diagnostic methods for studying the lymphatic system, there are isolated works on its morpho-functional state in chronic venous insufficiency. The purpose of the study was to study the anatomical and physiological state of the surface lymphatic system of the lower extremities in persons with different clinical classes of chronic vein diseases using fluorescence lifography. The study was conducted in 105 patients divided into six groups according to the clinical class of chronic diseases of the veins of the lower extremities according to the CEAP classification. We used fluorescent lymphography using sodium fluorescein to study the anatomical and functional capabilities of the lymphotone. The study revealed that morphofunctional changes in superficial lymphatic vessels in chronic lower extremity vein diseases depend on venous system decompensation. With an increase in the clinical class of chronic diseases of the veins of the lower extremities, the rate of lymph flow through the superficial lymphatic vessels is statistically significantly reduced. At the same time, the antegrade lymph cell is completely absent in C5-C6, with the appearance of retrograde outflow and discharge of the lymph into the deep lymph vessels. Thus, the progression of chronic venous insufficiency leads to proportional progression of morphofunctional changes in the superficial lymphatic system, which leads to the formation of lymphovenous insufficiency.

Keywords: varicose veins, chronic diseases of veins of lower extremities, chronic venous insufficiency, lymphatic vessels, lymphography, fluorescent lymphography, lymph cell.

Contacts: Abduvosidov Kh.A., email: sogdiana99@gmail.com

For citations: Abduvosidov Kh.A., Chudnykh S.M., Shestakova V.G., Alekseev A.G., Kokoev M.M., Kozlov N.S., Korolyuk G.M. Anatomical-functional state of surface lymphatic system of lower extremities in chronic vein diseases according to fluorescence lymphography, *Biomedical Photonics*, 2023, vol. 12, no. 4, pp. 15–21. doi: 10,24931/2413–9432–2023–12-4-15–21.

АНАТОМО-ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ПОВЕРХНОСТНОЙ ЛИМФАТИЧЕСКОЙ СЕТИ НИЖНИХ КОНЕЧНОСТЕЙ ПРИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЯХ ВЕН ПО ДАННЫМ ФЛУОРЕСЦЕНТНОЙ ЛИМФОГРАФИИ

Х.А. Абдувосидов[1, 2, 3], С.М. Чудных[2, 4], В.Г. Шестакова[3], А.Г. Алексеев[1], М.М. Кокоев[4], Н.С. Козлов[4], Г.М. Королюк[4]
[1]Российский биотехнологический университет, Москва, Россия
[2]Московский клинический научно-практический центр им. А.С. Логинова Департамента здравоохранения г. Москвы, Москва, Россия
[3]Тверской государственный медицинский университет, Тверь, Россия
[4]Московский государственный медико-стоматологический университет им. А.И. Евдокимова, Москва, Россия

Резюме

Несмотря на большой арсенал диагностических методов исследования лимфатической системы, имеются единичные работы, посвящённые морфофункциональному ее состоянию при хронической венозной недостаточности. Целью исследования явилось изучение анатомо-физиологического состояния поверхностной лимфатической сети нижних конечностей у лиц с разными клиническими классами хронических заболеваний вен при помощи флуоресцентной лимфографии. В исследование включены 105 пациентов, распределённых на шесть групп согласно клиническому классу хронических заболеваний вен нижних конечностей по классификации CEAP. Для исследования анатомо-функциональных возможностей лимфооттока нами использована методика флуоресцентной лимфографии с применением флуоресцеина натрия. При исследовании выявлено, что морфофункциональные изменения поверхностных лимфатических сосудов при хронических заболеваниях вен нижних конечностей зависят от декомпенсации венозной системы. При возрастании клинического класса хронических заболеваний вен нижних конечностей статистически достоверно уменьшается скорость лимфооттока по поверхностным лимфатическим сосудам. При этом антеградный лимфооттток полностью отсутствует у пациентов с классом хронических заболеваний вен нижних конечностей по классификации CEAP C5-C6, с появлением ретроградного оттока и сброса лимфы в глубокие лимфатические сосуды. Таким образом, прогрессирование хронической венозной недостаточности приводит к пропорциональному прогрессированию морфофункциональных изменений в поверхностной лимфатической системе, что вызывает формирование лимфовенозной недостаточности.

Ключевые слова: варикозная болезнь, хронические заболевания вен нижних конечностей, хроническая венозная недостаточность, лимфатические сосуды, лимфография, флуоресцентная лимфография, лимфооттток.

Контакты: Абдувосидов Х.А., email: sogdiana99@gmail.com

Для цитирования: Абдувосидов Х.А., Чудных С.М., Шестакова В.Г., Алексеев А.Г., Кокоев М.М., Козлов Н.С., Королюк Г.М. Анатомо-функциональное состояние поверхностной лимфатической сети нижних конечностей при хронических заболеваниях вен по данным флуоресцентной лимфографии // Biomedical Photonics. – 2023. – Т. 12, № 4. – С. 15–21. doi: 10,24931/2413–9432–2023–12-4-15–21.

Introduction

Chronic venous diseases of the lower extremities are one of the urgent problems in modern medicine. According to a number of authors, 80% of the population of industrialized countries suffers from these diseases, up to 50% of them have signs of chronic venous insufficiency (CVI), and up to 10% have trophic disorders of the lower extremities [1, 2, 3, 4, 5]. When venous outflow from the lower limb basin is disturbed, as some authors note, the function of the lymphatic system is also disturbed, which proves the close interrelation of these two systems. At pathological processes in the vein system of the lower limbs a vicious circle is created, which represents secondary compensatory morphofunctional changes in the lymphatic system, which subsequently take irreversible character [6].

To date, many techniques for studying the morphofunctional state of the lymphatic system has been developed. Back in the beginning of the last century, russian scientists A.S. Zolotukhin and M.G. Prives developed a technique of lifetime study of the lymphatic system – indirect lymphography. With the development of technologies the study of the lymphatic system was improved. Various ways of studying the lymphatic system with the help of radiation methods were introduced into medical practice [7, 8, 9]. Modern diagnostic methods allow to give morphofunctional characterization of the studied objects, but at the same time these methods are rather expensive and often invasive.

Today, various methods of lymphography, including fluorescence lymphography, are used worldwide. Most researchers point to the effectiveness of this method in patients with lymphedema to identify the causes of lymphatic channel dysfunction [10, 11, 12, 13, 14, 15]. At the same time, there are few studies in the literature, which are aimed at studying the lymphatic system in chronic venous insufficiency.

The aim of our study was to investigate the anatomo-physiological state of the superficial lymphatic network of the lower extremities in individuals with different clinical classes of chronic venous diseases using fluorescence lithography.

Materials and Methods

The study was approved by the independent ethics committee of the Moscow Clinical Research and Practice Center named after A.S. Loginov, Department of Public Health, Moscow (protocol No. 6/2021 of 23.06.2021). 105 patients were examined. There were 48 women and 57 men among the patients. Preliminarily, all patients underwent ultrasound duplex examination of the lower limb vessels to study the morphologic and functional status of both veins and arteries. Complaints and anamnesis were analyzed. Patients with oncological diseases, patients who had undergone occlusive thrombosis of deep veins of the lower extremities, as well as patients with diabetes mellitus and stenotic atherosclerosis of the arteries of the lower extremities were not included in the study. Depending on the clinical class of chronic vein diseases of the lower limbs according to the CEAP classification, the patients were categorized into six groups (Table 1).

To study the anatomy of superficial lymphatic vessels and functional capabilities of lymphatic outflow in real

Таблица 1
Распределение пациентов с разными клиническими классами хроническими заболеваниями вен (ХЗВ) по CEAP

Table 1
Distribution of patients with different clinical classes of chronic vein diseases (CVD) by CEAP

№ группы № group	CEAP	Количество пациентов Number of patients	Пол		Возраст Age
			M Male	Ж Female	
1	C-0; C-1	30	18	12	68 [64–72]
2	C-2	15	7	8	67 [61-73]
3	C-3	15	7	8	66 [63-74]
4	C-4	15	10	5	67 [59-72]
5	C-5	15	9	6	67 [64-72]
6	C-6	15	6	9	69 [63-73]
Всего Total		105	57	48	68 [63-73]

time, we applied the technique of fluorescence lymphography with the use of sodium fluorescein [16, 17].

The CEAP classification was adopted at the American phlebological forum in 1994. Later it was widely spread in Europe and Asia. Today this classification is widely used by the majority of phlebologists in Russia.

In our study we applied fluorescent lymphography using fluorescein preparation ("Novartis"), the active substance of which is diagnostic dye fluorescein sodium (Fig. 1). In the horizontal position of the patient, 2 ml of fluorescein sodium diluted 10 times in physiological solution was injected into the area of the first and second interfinger spaces and the area of the right and left ankle. After subcutaneous injection of the drug, an examination was performed using a light source with a blue spectrum of radiation (wavelength – 480 nm), stimulation of which leads to yellow-green fluorescence with a wavelength of 520 to 530 nm. After 5, 10, 15, 15, 30, 45, 60 min in dark room conditions using a light source with 480 nm wavelength, staining of superficial lymphatic vessels was assessed, followed by documentation with a digital camera. The number of visualized vessels, their topography, straightness of direction, as well as the width of luminescence and the direction of lymph flow through lymphatic vessels were evaluated (Fig. 2).

Using a stopwatch and a ruler, the lymph flow velocity along the superficial lymphatic vessels was measured, for which the length of the stained vessel and the time elapsed after fluorescein injection was measured in each of the specified time intervals. To calculate the lymph flow velocity the formula V=S/T was applied, where S is the length of the stained vessel, T is the time after the drug injection.

The Shapiro-Wilk method was used to determine the type of quantitative features. A sign was considered normally distributed at p>0.05. Quantitative data are presented as median and interquartile range (25% and 75%). Statistical analysis was performed using non-parametric statistical methods. The Kraskell-Wallis method (ANOVA) was used to compare the six groups. The sign was considered reliably different in the groups at p<0.05. When this condition was met, the Mann-Whitney method for pairwise comparisons with Bonferroni correction (k=0.05/15=0.0033) was further used.

Рис. 1. Флуоресцеин натрия и фонарь с излучением синего спектра.
Fig. 1. Fluorescein sodium and Blue Light.

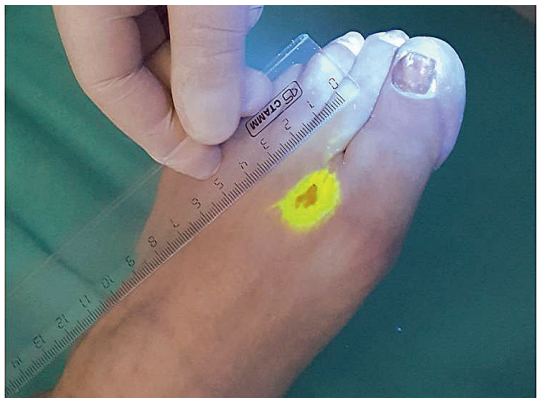


Рис. 2. Оценка степени лимфатической недостаточности после введения флуоресцеина натрия.
Fig. 2. Assessment of the degree of lymphatic insufficiency after fluorescein sodium injection.

Results and Discussion

Preliminary ultrasound examination showed that patients with clinical class 0 and 1 had no signs of valve insufficiency and varicose transformation of the lower limb veins. At the same time, clinically there were only signs of telangiectasias or reticular vein dilatation. The listed clinical and instrumental data and further investigation of lymphatic vessels by fluorescence lymphography showed that in group 1 patients the superficial lymphatic network consisted of rectilinear and uniform in diameter numerous drainage collectors.

After sodium fluorescein injection there was a clear fluorescence with the image of lymphatic vessels course, and during further 30-50 min there was a clear staining of superficial lymphatic network. In the first group of patients we noted that 1-2 min after the drug injection the injection site took a proximal elongated shape (Fig. 3). The velocity indices of lymph flow through superficial lymphatic vessels in the patients of the first group were the highest and amounted to 11.3 [10.9-11.5] cm/min (Table 3). When studying morphometric parameters in patients of this group the following data were obtained: vessel luminal width was equal to 2 [1.5-2.0] mm (Table 2).

Further study showed that in group 2 patients suffering from varicose veins without clinical signs of CVI, such as edema or trophic disorders, superficial lymphatic vessels took a tortuous shape. At the same time, the width of lymphatic vessels in patients of this group was 2 [2-2.5] mm, which was significantly greater compared to the parameters of group 1 patients (p=0.0016). In patients of the 2nd group three groups of direction of superficial collector lymphatic vessels, as well as the multiplicity of diverting collector lymphatic vessels were preserved in the tibia region. The functional state of the superficial lymphatic network in patients with CEAP class 2 was significantly lower than in group 1 patients, as indicated by a decrease in lymphatic outflow velocity to 8.3 [8.2-8.5] cm/min (p<0.0001 compared with group 1).

In patients with varicose disease with clinical manifestation in the form of lower limb edema without trophic disorders, the same number of superficial vessels in the lower leg area was preserved as in patients of groups 1 and 2. The course of the superficial lymphatic vessels was not straight, in the tibia region there was noted a tortuosity of their direction. At the same time it was revealed that in group 3 patients with the appearance of edema, which characterizes the beginning of venous insufficiency, the width of superficial lymphatic vessels luminescence increases, indicating morphological changes in lymphatic vessels. Thus, the luminal width in group 3 was the maximum, amounting to 3.5 [3.5-3.5] mm (p<0.001 compared with the values of groups 1 and 2). Parallel to the increase in the width of lymphatic vessels in patients of group 3, their functional state also deteriorated, which was indicated by a decrease in the antegrade lymph

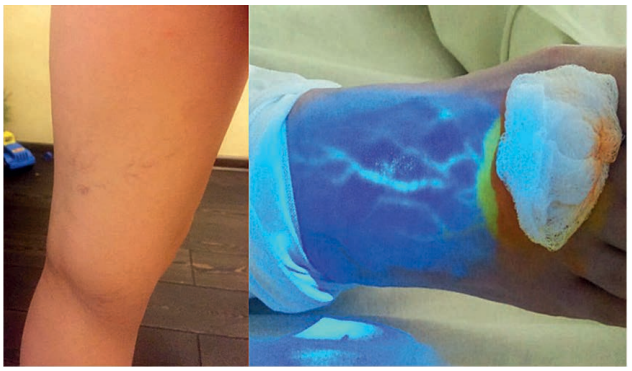


Рис. 3. Флуоресцентная лимфография у пациентки с 1-м клиническим классом ХЗВ по CEAP. Через 5 мин после введения флуоресцеина натрия окрашены лимфатические сосуды тыла правой стопы.
Fig. 3. Fluorescent lymphography in a patient with CVD Class 1 according to CEAP. 5 min after the injection of fluorescein sodium, lymph vessels of the rear of the right foot were stained.

Таблица 2
Морфологическая характеристика поверхностных лимфатических сосудов при различных клинических классах ХЗВ по CEAP

Table 2
Morphological characterization of superficial lymphatic vessels in different clinical CVD classes according to CEAP

Группы Groups	Ширина свечения сосуда (мм) Vessel glow width (mm)	P-value p<0,0001
1 (n-30)	2 [1,5-2,0]	P1-2 p=0,0016; P1-3 p<0,0001; P1-4 p<0,0001; P1-5 p=0,0044; P1-6 p<0,0001
2 (n-15)	2 [2-2,5]	P2-3 p<0,0001; P2-4 p<0,0001; P2-5 p=0,001; P2-6 p<0,0001
3 (n-15)	3,5 [3,5-3,5]	P3-4 p=0,0013; P3-5 p<0,0001; P3-6 p<0,0001
4 (n-15)	3,0 [3,0-3,5]	P4-5 p<0,0001; P4-6 p<0,0001
5 (n-15)	1,0 [0,5-2,0]	P5-6 p=0,23
6 (n-15)	1,0 [0,5-1,5]	

*Для сравнения шести групп применяли метод Краскела-Уоллиса. Признак считали достоверно отличным в группах при p<0,05, При выполнении этого условия далее использовали метод Манна-Уитни для парных сравнений с поправкой Бонферрони (k=0,05/15=0,0033)
*The Kraskel-Wallis method was used to compare the six groups. The sign was considered significantly different in groups at p < 0,05, Under this condition, the Mann-Whitney method was further used for Bonferroni-corrected pairwise comparisons (k = 0,05/15 = 0,0033)

Таблица 3
Функциональная характеристика поверхностных лимфатических сосудов при различных клинических классах ХЗВ по CEAP

Table 3
Functional characteristics of superficial lymphatic vessels in different clinical CVD classes according to CEAP

Группы Groups	Скорость лимфотока (см/мин) Lymph flow rate (cm/min)	P-value p<0,0001
1 (n-30)	11,3 [10,9-11,5]	P1-2, P1-3, P1-4, P1-5, P1-6 p<0,0001
2 (n-15)	8,3 [8,2-8,5]	P2-3, P2-4, P2-5, P2-6 p<0,0001
3 (n-15)	4,7 [4,6-5,7]	P3-4, P3-5, P3-6 p<0,0001
4 (n-15)	1,3 [1-1,6]	P4-5, P4-6 p<0,0001
5 (n-15)	0,6 [0,4-0,8]	P5-6 p=0,19
6 (n-15)	0,5 [0-0,6]	

flow rate to 4.7 [4.6-5.7] cm/min (p<0.0001 compared to groups 1 and 2).

Patients included in group 4 had edema of varying severity and trophic disorders in the form of indurative changes of the skin and subcutaneous tissue or lipodermatosclerosis. Trophic disorders in the majority of patients in this group had a circular character. The study revealed that in this group of patients the width of vessels was uneven, along the course of vessels their dilation and constriction, as well as tortuosity of lymphatic vessels on the foot were noted (Fig. 4). The luminescence width of superficial lymphatic collectors in this group of patients was 3.0 [3.0-3.5] mm (p<0.0001 compared to the values of patients in the previous groups). At fluorescence lymphography in the area of trophic disorders, the contrast of superficial lymphatic vessels was not not observed. At the same time, patients with the 4th clinical class showed pronounced disorders of the functional state of the lymphatic network of the lower limbs, which was indicated by a significant decrease in the antegrade lymph flow rate to 1.3 [1.0-1.6] cm/min (p<0.0001 compared to the previous groups). When sodium fluorescein was injected into the ankle region, the staining of lymphatic vessels in this group of patients occurred in a retrograde direction. The established retrograde current of sodium fluorescein from the ankles was at a rate of 2.9 [1.5-3.1] cm/min.

Patients with a history of trophic ulcers on the background of CVI were included in group 5, and patients with open trophic ulcers in the shin area – in group 6. During the examination it was revealed that patients of groups 5 and 6 also had uneven diameter of superficial lymphatic vessels on the background of trophic disorders (as well as patients of groups 3 and 4). The width of vessels was narrowed, and their course was not straight on the back of the foot in the form of tortuosity of the vascular network. The luminal width of vessels in patients of groups 5-6 was statistically significantly (p<0.0033 with Bonferroni correction) smaller compared to the values of patients of groups 1-4, amounting to 1.0 [0.5-2.0] mm and 1.0 [0.5-1.5] mm, respectively. It should be noted that no fluorescence of lymphatic vessels was detected in the area of pronounced indurative changes and trophic ulcers when performing lymphography, which indicated sclerosing of lymphatic vessels against the background of scarring changes of soft tissues. At the same time in patients of these groups against the background of expressed trophic disorders there was a significant decrease of lymph flow velocity along the superficial lymphatic vessels (Table 3). The lymph flow velocity was equal to 0.6 [0.4-0.8] cm/min, and 0.5 [0.0-0.6] cm/min, respectively. When

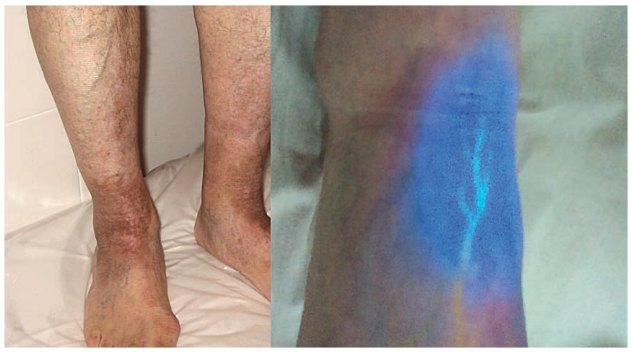


Рис. 4. Флуоресцентная лимфография у пациента с 4-м клиническим классом ХЗВ по CEAP. Через 15 мин после введения флуоресцеина натрия окрашены лимфатические сосуды тыла стопы, переходящие в медиальную группу коллекторов.
Fig. 4. Fluorescence lymphography in a patient with CVD class 4 according to CEAP. 15 min after the injection of fluorescein sodium, the lymph vessels of the rear of the foot were stained, passing into the medial group of collectors.

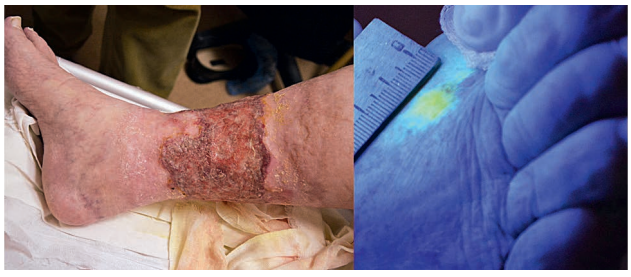


Рис. 5. Флуоресцентная лимфография у пациента с 6-м клиническим классом ХЗВ по CEAP. Через 5 мин после введения флуоресцеина натрия происходит окрашивание в ретроградном направлении.
Fig. 5. Fluorescence lymphography in a patient with CVD 6 clinical class according to CEAP. 5 min after the injection of fluorescein sodium, retrograde staining occurs.

sodium fluorescein was administered, it was observed that staining of lymphatic vessels occurred in the retrograde direction, and the lymphatic current velocity was 1.5 [1.2-1.7] cm/min, 1.2 [1.1-1.7] cm/min in the retrograde direction, respectively (Figure 5).

There are single works in the literature, which are devoted to the study of the functional state of the lymphatic network of patients with chronic venous insufficiency of the lower extremities [18, 19]. Using functional lymphography with the use of superfluid oil lipidol preparation and lymphoscintigraphy, G.V. Chepelenko a violation of drainage and transport function of lymphatic capillaries was established from the edges of the ulcer, at the level of withdrawing (from the skin to the collector), collecting (from the foot to the regional nodes) vessels [18]. We have developed and patented the technique of fluorescent lymphography [16, 17, 19], which was used to study superficial lymphatic vessels in individuals with different clinical classes of CVD according to CEAP classification. On the basis of the performed study using fluorescent lymphography a close relationship between secondary changes in the lymphatic channel of the lower limbs and the severity of trophic disorders on the background of chronic venous insufficiency was revealed. It was found out that the antegrade lymph flow rate through superficial lymphatic vessels decreases in proportion to the increase of clinical class according to CEAP and is completely absent at C5-C6, which is explained by retrograde flow and lymph discharge into deep lymphatic vessels. The course of varicose veins is manifested by deterioration of functional state of lymphatic vessels, which leads to decompensated state of lymphatic outflow.

Conclusion

Thus, the progression of chronic venous insufficiency leads to proportional deterioration of the morphofunctional state of the superficial lymphatic system, which leads to the formation of lymphovenous insufficiency.

REFERENCES

1. Mazaishvili K.V., Kiyan K.A., Sukhanov A.V., Shiriyazdanova Yu.F. Prevalence and compatibility of chronic venous disorders of the lower extremities, restless legs syndrome, anxiety and depressive states among employees of enterprises in the Moscow region. *Phlebology*, 2019, vol.13(1), pp. 12-20. doi 10.17116/flebo20191301112.
2. Kirsten N., Mohr N., Gensel F., Alhumam A., Bruning G., Augustin M. Population-Based Epidemiologic Study in Venous Diseases in Germany – Prevalence, Comorbidity, and Medical Needs in a Cohort of 19,104 Workers. *Vasc Health Risk Manag*, 2021, vol. 17, pp. 679-687. doi:10,2147/VHRM.S323084
3. Rabe E., Guex J.J., Puskas A., Scuderi A., Fernandez Quesada F; VCP Coordinators. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. *Int Angiol*, 2012, vol. 31(2), pp. 105-115.
4. Vuylsteke M.E., Thomis S., Guillaume G., Modliszewski M.L., Weides N., Staelens I. Epidemiological study on chronic venous disease in Belgium and Luxembourg: prevalence, risk factors, and symptomatology. *Eur J Vasc Endovasc Surg*, 2015, vol. 49(4), pp. 432-439. doi: 10,1016/j.ejvs.2014.12.031
5. Zolotukhin I.A., Seliverstov E.I., Shevtsov Y.N., Avakiants I.P., Nikishkov A.S., Tatarintsev A.M., Kirienko A.I. Prevalence and Risk Factors for Chronic Venous Disease in the General Russian Population. *Eur J Vasc Endovasc Surg*, 2017, vol. 54(6), pp.752-758. doi: 10,1016/j.ejvs.2017.08.033
6. Chepelenko G.V. The role of the lymphatic system in potentiating the clinical stages of chronic venous insufficiency of the lower extremities. *Angiology and vascular surgery,* 2004, vol. 10(2), pp. 124-128.
7. Potashov L.V. et al. Surgical lymphology. – St. Petersburg: Publishing house of St. Petersburg GETU "LETI", 2000, vol. 270. pp. 80-86.
8. Limashova Yu.B., Chernova V.I. National guidelines for radionuclide diagnostics / Tomsk: TT, 2010, vol. 2, p. 418.
9. Levanovich V.V., Yalfimov A.N., Kanina L.Ya., etc. A method for diagnosing lymphedema of the extremities. Patent No. 2577766 C1, IPC A61B 5/055, A61K 49/06.
10. Yarema I.V., Polsachev V.I., Mushnikova N.Yu. Fluorescent lymphography as a method of visualization of the lymphatic

ЛИТЕРАТУРА

1. Мазайшвили К.В., Киян К.А., Суханов А.В., Ширияданова Ю.Ф. Распространенность и сочетаемость хронических венозных расстройств нижних конечностей, синдрома беспокойных ног, тревоги и депрессивных состояний среди работников предприятий Московского региона // Флебология. – 2019. – Т.13, №1. – С. 12-20. doi 10.17116/flebo20191301112.
2. Kirsten N., Mohr N., Gensel F., Alhumam A., Bruning G., Augustin M. Population-Based Epidemiologic Study in Venous Diseases in Germany – Prevalence, Comorbidity, and Medical Needs in a Cohort of 19,104 Workers // Vasc Health Risk Manag. – 2021. – Vol. 17. – P. 679-687. doi:10,2147/VHRM.S323084
3. Rabe E., Guex J.J., Puskas A., Scuderi A., Fernandez Quesada F; VCP Coordinators. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program // Int Angiol. – 2012. – Vol. 31(2). – P. 105-115.
4. Vuylsteke M.E., Thomis S., Guillaume G., Modliszewski M.L., Weides N., Staelens I. Epidemiological study on chronic venous disease in Belgium and Luxembourg: prevalence, risk factors, and symptomatology // Eur J Vasc Endovasc Surg. – 2015. – Vol. 49(4). – P. 432-439. doi: 10,1016/j.ejvs.2014.12.031
5. Zolotukhin I.A., Seliverstov E.I., Shevtsov Y.N., Avakiants I.P., Nikishkov A.S., Tatarintsev A.M., Kirienko A.I. Prevalence and Risk Factors for Chronic Venous Disease in the General Russian Population // Eur J Vasc Endovasc Surg. – 2017. – Vol. 54(6). – P. 752-758. doi: 10,1016/j.ejvs.2017.08.033
6. Чепеленко Г.В. Роль лимфатической системы в потенцировании клинических стадий хронической венозной недостаточности нижних конечностей // Ангиология и сосудистая хирургия. – 2004. – Т.10, №2. – С. 124-128.
7. Поташов Л.В. и др. // Хирургическая лимфология. – СПб: Изд-во СПб ГЭТУ «ЛЭТИ» . – 2000. – Т.270. – С. 80-86.
8. Лимашова Ю.Б., Чернова В.И. Национальное руководство по радионуклиидной диагностике / Томск: ТТ . – 2010 . – Т. 2. – С. 418.
9. Леванович В.В., Ялфимов А.Н., Канина Л.Я. и др. Способ диагностики лимфедем конечностей // Патент № 2577766 С1, МПК А61В 5/055, А61К 49/06.
10. Ярема И.В., Полсачев В.И., Мушникова Н.Ю. Флюоресцентная лимфография как метод визуализации лимфатической

system. The first experience. *Surgeon*, 2012, vol. 4, pp. 24-26. – EDN SGZZLT

11. Keo H.H., Husmann M., Groechenig E., Willenberg T., Gretener S.B. Diagnostic accuracy of fluorescence microlymphography for detecting limb lymphedema. *Eur J Vasc Endovasc Surg*, 2015, vol. 49(4), pp. 474-479. doi:10.1016/j.ejvs.2014.12.033
12. Yamamoto T., Yoshimatsu H., Narushima M., Yamamoto N., Hayashi A., Koshima I. Indocyanine Green Lymphography Findings in Primary Leg Lymphedema. *Eur J Vasc Endovasc Surg*, 2015, vol. 49(1), pp. 95-102. doi:10,1016/j.ejvs.2014.10.023
13. Unno N., Nishiyama M., Suzuki M., et al. Quantitative lymph imaging for assessment of lymph function using indocyanine green fluorescence lymphography. *Eur J Vasc Endovasc Surg*, 2008, vol. 36(2), pp. 230-236. doi:10,1016/j.ejvs.2008.04.013
14. Proulx S.T., Luciani P., Derzsi S., et al. Quantitative imaging of lymphatic function with liposomal indocyanine green. *Cancer Res*, 2010, vol. 70(18), pp. 7053-7062. doi:10.1158/0008-5472.CAN-10-0271
15. Rasmussen J.C., Aldrich M.B., Guilliod R., Fife C.E., O'Donnell T.F., Sevick-Muraca E.M. Near-infrared fluorescence lymphatic imaging in a patient treated for venous occlusion. *J Vasc Surg Cases*, 2015, vol. 1(3), 201-204. doi:10,1016/j.jvsc.2015.05.004
16. Yarema V.I., Fatuev O.E., Abduvosidov H.A. and others. The lymphatic system of the lower extremities in chronic venous insufficiency. *Surgeon*, 2016, vol. 1, pp. 10-20.
17. Yarema V.I., Abduvosidov H.A., Fatuev O.E. and others. A method for the lifetime study of anatomical and physiological features of the superficial lymphatic vessels of the lower extremities in normal and chronic venous insufficiency. Patent No. 2705235 C1, IPC A61B 5/0215, A61K 49/00, A61P 43/00.
18. Chepelenko G.V. Functional assessment of the lymphatic bed in patients with late clinical classes of chronic venous insufficiency according to the international classification of CEAR. *Angiology and vascular surgery*, 2006, vol. 12(4), pp. 95-102.
19. Yarema V.I., Abduvosidov H.A., Makeeva E.A., Karchevskaya V.A. Application of the fluorescence lymphography method for the lifetime study of the anatomy of the superficial lymphatic vessels of the lower extremities. *Morphological bulletin*, 2017, vol. 25(2), pp. 69-71. doi 10,20340/mv-mn.17(25).02.15

системы. Первый опыт / Хирург. – 2012. – № 4. – С. 24-26. – EDN SGZZLT

11. Keo H.H., Husmann M., Groechenig E., Willenberg T., Gretener S.B. Diagnostic accuracy of fluorescence microlymphography for detecting limb lymphedema // Eur J Vasc Endovasc Surg. – 2015. – Vol. 49(4). – P. 474-479. doi:10.1016/j.ejvs.2014.12.033
12. Yamamoto T., Yoshimatsu H., Narushima M., Yamamoto N., Hayashi A., Koshima I. Indocyanine Green Lymphography Findings in Primary Leg Lymphedema // Eur J Vasc Endovasc Surg. – 2015. – Vol. 49(1). – P. 95-102. doi:10,1016/j.ejvs.2014.10.023
13. Unno N., Nishiyama M., Suzuki M., et al. Quantitative lymph imaging for assessment of lymph function using indocyanine green fluorescence lymphography // Eur J Vasc Endovasc Surg. – 2008. – Vol. 36(2). – P. 230-236. doi:10,1016/j.ejvs.2008.04.013
14. Proulx S.T., Luciani P., Derzsi S., et al. Quantitative imaging of lymphatic function with liposomal indocyanine green // Cancer Res. – 2010. – Vol. 70(18). – P. 7053-7062. doi:10.1158/0008-5472.CAN-10-0271
15. Rasmussen J.C., Aldrich M.B., Guilliod R., Fife C.E., O'Donnell T.F., Sevick-Muraca E.M. Near-infrared fluorescence lymphatic imaging in a patient treated for venous occlusion // J Vasc Surg Cases. – 2015. – Vol. 1(3). – P. 201-204. doi:10,1016/j.jvsc.2015.05.004
16. Ярема В.И., Фатуев О.Э., Абдувосидов Х.А. и др. Лимфатическая система нижних конечностей при хронической венозной недостаточности // Хирург. – 2016. – № 1. – С. 10-20.
17. Ярема В.И., Абдувосидов Х.А., Фатуев О.Э. и др. Способ прижизненного изучения анатомо-физиологических особенностей поверхностных лимфатических сосудов нижних конечностей в норме и при хронической венозной недостаточности // Патент № 2705235 С1, МПК А61В 5/0215, А61К 49/00, А61Р 43/00.
18. Чепеленко Г.В. Функциональная оценка лимфатического русла больных с поздними клиническими классами хронической венозной недостаточности по международной классификации СЕАР // Ангиология и сосудистая хирургия. – 2006. – Т.12. №4. – С. 95-102.
19. Ярема В.И., Абдувосидов Х.А., Макеева Е.А., Карчевская В.А. Применение метода флюоресцентной лимфографии для прижизненного изучения анатомии поверхностных лимфатических сосудов нижних конечностей // Морфологические ведомости. – 2017. – Т. 25, № 2. – С. 69-71. doi 10,20340/mv-mn.17(25).02.15

PHOTODYNAMIC THERAPY OF BOWEN'S DISEASE

Filonenko E.V.[1], **Ivanova-Radkevich V.I.**[2]
[1]P.A. Herzen Moscow Oncology Research Center – branch of FSBI NMRRC of the Ministry of Health of the Russian Federation, Moscow, Russia
[2]Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Abstract

Bowen's disease is a form of non-invasive (*in situ*) squamous cell skin cancer localized in the non-genital area. Russian and European clinical guidelines include photodynamic therapy (PDT) in the standard of care for patients with Bowen's disease. In the present review, the efficacy and safety profile of different PDT regimens for Bowen's disease are analyzed according to the available literature data. PDT can be used to treat large Bowen's disease lesions localized in areas of the body characterized by severe healing and in cases where surgery is not feasible. Analysis of the results of studies shows that PDT is superior in efficacy and cosmetic results to traditional local treatments such as 5-fluorouracil or cryotherapy. In all analyzed studies in patients with Bowen's disease, PDT achieved a significant clinical effect. Complete regression of pathologic foci was achieved in 67-100% of patients. In studies evaluating the recurrence rate of Bowen's disease after PDT, this value ranged from 2-28% with the range of 6-18% in most of the studies. Most often, 5-aminolevulinic acid and its methyl ester are used for PDT in Bowen's disease. According to some researchers, aminolevulinic acid allows to achieve a more long-term positive clinical effect with a lower incidence of painful reactions during treatment.

Key words: photodynamic therapy, Bowen's disease, 5-aminolevulinic acid, 5-aminolevulinic acid methyl ester.

Contacts: Filonenko E.V., e-mail: elena.filonenko@list.ru

For citations: Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy of Bowen's disease, *Biomedical Photonics*, 2023, vol. 12, no. 4, pp. 22–29. doi: 10.24931/2413–9432–2023–12-4-22–29.

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПАЦИЕНТОВ С БОЛЕЗНЬЮ БОУЭНА

Е.В. Филоненко[1], **В.И. Иванова-Радкевич**[2]
[1]«Московский научно-исследовательский онкологический институт им. П.А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации, Москва, Россия
[2]Российский Университет дружбы народов, Москва, Россия

Резюме

Болезнь Боуэна – форма неинвазивного (*in situ*) плоскоклеточного рака кожи, локализованная в негенитальной области. Российские и европейские клинические рекомендации включают фотодинамическую терапию (ФДТ) в стандарты лечения пациентов с болезнью Боуэна. В настоящем обзоре по имеющимся литературным данным проанализированы эффективность и профиль безопасности различных схем применения ФДТ при болезни Боуэна. ФДТ может быть применена для воздействия на очаги болезни Боуэна большого размера, локализованные на участках тела, характеризующихся тяжелым заживлением, а также в случаях, когда хирургическое вмешательство представляется нецелесообразным. Анализ результатов исследований показывает, что ФДТ превосходит по эффективности и косметическим результатам традиционные местные методы лечение, такие как применение 5-фторурацила или криотерапию. Во всех проанализированных исследованиях у пациентов с болезнью Боуэна, ФДТ позволила достичь значимого клинического эффекта. Полная регрессия патологических очагов была достигнута у 67-100% пациентов. В исследованиях, оценивавших частоту рецидивов болезни Боуэна после ФДТ, значение этого показателя составляло 2-28%, в большинстве исследований 6-18%. Чаще всего для ФДТ при болезни Боуэна применяют 5-аминолевулиновую кислоту и ее метиловый эфир. По данным некоторых исследователей аминолевулиновая кислота позволяет достичь более долгосрочного положительного клинического эффекта с меньшей частотой развития болевых реакций в процессе лечения.

Ключевые слова: фотодинамическая терапия, болезнь Боуэна, плоскоклеточный рак кожи in situ, 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты.

Контакты: Филоненко Е.В., e-mail: elena.filonenko@list.ru

Для цитирования: Филоненко Е.В., Иванова-Радкевич В.И. Фотодинамическая терапия пациентов с болезнью Боуэна // Biomedical Photonics. – 2023. – Т. 12, № 4. – С. 22–29. doi: 10.24931/2413–9432–2023–12-4-22–29.

Introduction

Bowen's disease (first described in 1912) is a form of intraepidermal (*in situ*) squamous cell skin cancer (SCSC). In addition to Bowen's disease, non-invasive forms of SCSC also include Keir's erythroplasia. According to current concepts, Bowen's disease is an *in situ* SCSC for lesions located in non-genital areas [1,2]. In Bowen's disease, if untreated, pathologic foci continue to slowly increase in size and may develop into an invasive form of SCSC after many years [2].

Etiology and pathogenesis

The factors that provoke the development of Bowen's disease include [2]:

- various types of irradiation (ultraviolet radiation, radiation therapy)
- local action of carcinogenic compounds (e.g., arsenic)
- immunosuppressors (in particular, various drugs with immunosuppressive effects)
- viruses (in a systematic review by Namgoong S. et al. human papillomavirus (HPV) was found in 28.3% of 904 extragenital in situ specimens of SCSC, with HPV-16 being the most common, followed by HPV-30 [3])
- chronic trauma
- dermatoses (e.g., common or chronic lupus erythematosus)
- seborrheic keratoses

etc.

Bowen's disease develops slowly, but can progress to invasive SCSC in about 10% of patients if not adequately treated. At the same time, cases of SCSC developed in patients with Bowen's disease are often more aggressive than those arising in actinic keratoses [4].

Clinical manifestations

There are certain difficulties in diagnosing Bowen's disease when differentiating it from various dermatoses. This is due to the fact that Bowen's disease often has no specific clinical manifestations [5].

Pathologic foci in Bowen's disease are usually well-defined, asymptomatic erythematous hyperkeratotic plaques with irregular well-defined borders, with tightly seated dry scales on the surface. Foci appear more often on areas of skin exposed to the sun, usually in light-skinned people. The pigmented variant of Bowen's disease occurs in 1.7-5.5% of cases, mostly in men with darker skin types, on sun-protected areas such as the lower extremities [2].

One of the first signs to suspect Bowen's disease may be the absence of any response to topical anti-inflammatory therapy [1,2].

At the onset of the disease, a small red spot (or several spots) is observed on the skin, the surface of which is covered with scales. The latter are easily removed from the surface of the spot. Under the removed scales, a foci with a moist and red surface is exposed, not accompanied by subjective sensations. With disease progression, the lesion thickens, an infiltrate appears, and in its place a dense plaque with clear even boundaries is formed, which can grow, become voluminous and rise above the skin [2,5].

There are four clinical forms of Bowen's disease [5]:

- anular, in which the plaque forms in the shape of a circle;
- verrucous, in which wart-like growths appear on the surface;
- pigmented in the form of a plaque of dark color (due to the content of a large amount of melanin);
- acral form, accompanied by skin lesions of the nail plate (more often on the lower extremities).

Diagnosis

Dermatoscopic examination is necessary to confirm the diagnosis of Bowen's disease. Bowen's disease usually shows superficial areas of scaling, tortuous vessels ("glomerular" vessels) and/or red clots ("globular" vessels), and small brown dots and globules in the pigmented variant. If there is doubt about the diagnosis or if confirmation is required before a particular treatment, the patient may be scheduled for a punch biopsy to histologically reveal full thickness epidermal dysplasia [1,2].

Therapy

Surgical removal

Standard surgical excision of a focus of Bowen's disease is recommended when there is diagnostic uncertainty regarding the invasiveness of the disease, as well as in the recurrent form of the disease and in immunocompromised patients. When performing surgical removal, it is advisable to remove the pathologic focus with a reserve of 3-5 mm [1,2].

In cases where it is important to preserve healthy tissue as much as possible (e.g., when removing a pathologic focus in the eye area or nail plate), Mohs micrographic surgery is the preferred option for surgical removal [2].

If surgical treatment is not possible (e.g., due to patient refusal of treatment, severe patient condition, or unsatisfactory expected cosmetic results with surgery), one of the local therapy options is recommended: curettage and electrocoagulation, radiation therapy, cryodestruction, photodynamic therapy, or local drugs with antitumor activity [1,2,5,6].

Local drug therapy

In Bowen's disease with small lesions (less than 2 cm), local application of 5% of 5-fluorouracil 1-2 times a day for 3-4 weeks is recommended. This therapy may cause

local side effects in the form of local inflammation, skin ulceration at the sites of application, and scarring at the site of lesions. In some cases, topical application of 5-fluorouracil is possible for larger lesions located in low-risk areas [1,2].

According to the clinical guidelines of the British Association of Dermatologists, local application of 5-fluorouracil cannot be recommended directly, but may be considered as an alternative to other treatments (e.g., if the patient refuses other treatments) in patients with large, localized lesions in areas where healing is usually difficult (e.g., shins in elderly patients) and in immunocompromised patients for the treatment of multiple and recurrent lesions [2,7-10].

Among other topical agents, 5% imiquimod may be recommended in patients with Bowen's disease (usually only if other alternative treatments are not possible) [2].

Cryodestruction

Cryodestruction may be recommended as a first-line treatment option for patients with small (<2 cm) *in situ* SCSC lesions [2,7,9]. One cycle of cryotherapy with freezing for 20-30 s or two cycles of 10-20 s is used to treat lesions in Bowen's disease. According to the British Association of Dermatologists, cryotherapy may be associated with greater discomfort, poorer healing, and more recurrences compared with scraping with cauterization. The use of cryotherapy in patients with Bowen's disease with large lesions or lesions located on the shin (higher probability of non-healing ulcers) and in immunocompromised patients is possible but should be considered on an individual basis [2,9].

Curettage with cauterization

Curettage with cauterization is mainly used to treat patients with small foci of Bowen's disease [2]. After the procedure, ulceration and prolonged healing of postoperative wounds are possible, so the age of the patient, general skin condition, localization and size of the lesion should be taken into account when prescribing this type of therapy. Besides, it is possible to use curettage with cauterization in immunocompromised patients [2].

Laser irradiation

Laser irradiation to target foci of Bowen's disease is used when other treatments have been ineffective or are not appropriate for the patient. The ablative CO_2 laser is considered more effective than the non-ablative neodymium:YAG laser [2].

Radiation therapy

Radiation therapy is performed only in immunocompetent patients with Bowen's disease, usually when the lesion is recurrent or unresponsive to other treatments, or when surgery is inappropriate or of a high risk [2].

Photodynamic therapy

In recent years, the use of non-invasive therapies has attracted increasing attention in the treatment of cancer and precancerous lesions. Photodynamic therapy (PDT) is one such conservative and non-invasive methods. During PDT, antitumor immune responses are triggered by nontoxic photosensitizers selectively accumulated in pathological tissue, which convert oxygen into cytotoxic reactive oxygen species under the action of light of a certain wavelength [11].

Numerous studies have confirmed that PDT demonstrates high efficacy with excellent cosmetic results in the treatment of superficial basal cell skin cancer [12], actinic keratosis [13], SCSC *in situ*, including genital localization [14], extramammary Paget's cancer [15], mycosis fungoides [16], and other tumor and pre-tumor diseases.

The aim of this review is to analyze the efficacy and safety profile of different PDT regimens for Bowen's disease.

The efficacy of PDT for Bowen's disease is considered to be equivalent or superior to local application of 5-fluorouracil and cryotherapy [9,8,10]. The cosmetic outcome with PDT is considered to be better compared to standard therapy. PDT can be used to treat large lesions, lesions localized to areas of the body characterized by severe healing, and in cases where surgery is not feasible [17].

In 2016 the American Society for Dermatologic Surgery approved protocols for the treatment of patients with Bowen's disease by PDT [4]:

- 5-aminolevulinic acid (5-ALA) topically, incubation time 4 h, irradiation with a red light source, light dose >100 J/cm^2;
- 5-ALA methyl ester (MAL) topically, incubation time 3 h, irradiation with red light source, light dose 75-100 J/cm^2.

The performed literature analysis allowed to identify 10 studies of PDT efficacy and safety in patients with Bowen's disease since 2000, in which 20 or more (up to 335) patients have been included (see Table). Studies in which PDT was performed in combination with other therapies were not included in the analysis, as the results of such studies do not allow estimating the contribution to the efficacy of PDT specifically.

In 3 studies out of those included in the analysis 5-ALA was used for PDT, in 6 – MAL, in 1 study – in part of patients 5-ALA, and in other part – MAL. The most frequent light dose in the studies was 37-75 J/cm^2, and 100-105 J/cm^2 in 2 studies. The number of performed PDT courses was usually 1-2, but in some studies it reached 6.

Effectiveness of PDT in Bowen's disease

As can be seen from the Table, in all studies in patients with Bowen's disease, PDT achieved a significant clinical effect. Complete regression of pathologic foci was

Таблица
Сводные данные результативности применения фотодинамической терапии у пациентов с болезнью Боуэна
Table
Summary of the effectiveness of photodynamic therapy in patients with Bowen's desease

Авторы Authors	Число пациентов* / количество очагов / No. of patients/ No. of lesions	Фотосенсибилизатор Photosensitizer	Режим облучения Light wavelength	Количество курсов ФДТ Number of PDT courses	Эффективность ФДТ PDT efficiency	Нежелательные реакции Adverse reactions
Varma et al., 2001 [18]	Нет данных/48	5-АЛК 5-ALA	105 Дж/см^2 105 J/cm^2	Нет данных No data	Полный эффект после 2 курсов 88%. Через 12 мес эффект сохранился у 69%. Full effect after 2 courses in 88%. After 12 months, the effect was maintained in 69%.	Нет данных No data
Salim et al., 2003 [8]	20/33	5-АЛК 5-ALA	100 Дж/см^2 100 J/cm^2	1-2 курса с интервалом 6 нед 1-2 courses with an interval of 6 weeks	Полный эффект 66,6% (после 1 курса) и 88% (после 2 курсов). Частота рецидивов 6%. Full effect in 66.6% (after 1 course) and in 88% (after 2 courses). Recurrence rate 6%.	Нет данных No data
Morton et al., 2006 [7]	90/111	МЭ-АЛК MAL	75 Дж/см^2 75 J/cm^2	2 курса с интервалом 1 нед. Повтор лечения через 3 мес в случае частичного эффекта 2 courses with an interval of 1 week. Repeat treatment after 3 months in case of partial effect	Частота клинического ответа 73% после двух курсов, 93% после 4 курсов. Частота рецидивов 15%. Хороший или отличный косметический результат в 97% случаев через 12 мес после лечения. Clinical response rate of 73% after 2 courses, 93% after 4 courses. Relapse rate 15%. Good or excellent cosmetic result in 97% of cases 12 months after treatment.	Нет данных No data
de Haas et al., 2007 [19]	40/50	5-АЛК 5-ALA	Сравнение двух схем облучения: 1) Однократное облучение (75 Дж/см^2) 2) Двукратное облучение (20 + 80 Дж/см^2) с 2-часовым интервалом затемнения Comparison of two irradiation schemes: 1) Single irradiation (75 J/cm^2) 2) Double irradiation (20 + 80 J/cm^2) with a 2-hour darkening interval	Нет данных No data	Полный эффект 80% (для схемы однократного облучения) и 88% (для схемы двукратного облучения). The total effect in 80% (for a single irradiation scheme) and in 88% (for a double irradiation scheme).	В группе с двукратным облучением у 5 пациентов зарегистрированы болевые ощущения во время сеанса облучения. In the group with double irradiation, 5 patients reported pain during the irradiation session.

Calzavara-Pinton et al., 2008 [20]	Нет данных/41 No data/41	МЭ-АЛК MAL	37 Дж/см^2 37 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полный эффект 87,8%. Частота рецидивов 17,1%. Full effect 87.8%. Recurrence rate 17.1%.	Нет данных No data
Cavicchini et al., 2011 [21]	30/43	МЭ-АЛК MAL	75 Дж/см^2 75 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полный эффект 100%. Частота рецидивов 16,7%. Full effect 100%. Recurrence rate 16.7%.	Хорошая переносимость, ощущение покалывания и жжения от умеренной до сильной степени во время облучения (93% пациентов) Well tolerated, moderate to severe tingling and burning sensation during radiation (93% of patients)
Truchuelo et al., 2012 [22]	47/51	МЭ-АЛК MAL	38 Дж/см^2 38 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полный эффект после двух курсов 76%. Частота рецидивов 14,3%. Превосходных косметический результат. The full effect after two courses is 76%. Recurrence rate – 14.3%. Excellent cosmetic results.	Чаще всего из нежелательных явлений – чувство жжения в момент лечения. The most common side effect is a burning sensation during treatment.
Ratour-Bigot et al., 2016 [23]	64/64	МЭ-АЛК MAL	Нет данных No data	1-6 курсов 1-6 courses	Полный эффект 52%. Частота рецидивов не оценена. Full effect 52%. Recurrence rates have not been assessed.	Нет данных No data
Zaar et al., 2017 [24]	335/423	МЭ-АЛК MAL	37 Дж/см^2 37 J/cm^2	1-2	Полный эффект 77,5%. Частота рецидивов 18,3%. Full effect in 77.5%. Recurrence rate – 18.3%.	Образование рубцов – 8,8%, эритема –6%, гипопигментация – 2,4%, гиперпигментация – 2,0% Scar formation – 8.8%, erythema -6%, hypopigmentation – 2.4%, hyperpigmentation – 2.0%
Alique-García et al., 2019 [25]	171/191	5-АЛК (55 очагов), МЭ-АЛК (136 очагов) 5-ALA (55 lesions), MAL (136 lesions)	37 Дж/см^2 37 J/cm^2	2 курса с интервалом 1 нед. Повтор лечения через 3 мес в случае частичного эффекта 2 courses with an interval of 1 week. Repeat treatment after 3 months in case of partial effect	ФДТ с 5-АЛК: полный эффект 87%; частота рецидивов 2%, через 12 мес эффект сохранился у 85%. ФДТ с МЭ-АЛК: полный эффект 76%; частота рецидивов 28%, через 12 мес эффект сохранился у 55%. PDT with 5-ALA: full effect in 87%; recurrence rate – 2%, after 12 months the effect was maintained in 85%. PDT with MAL: full effect in 76%; recurrence rate – 28%, after 12 months the effect was maintained in 55%.	У 5% пациентов, в группе 5-АЛК и у 2% пациентов в группе МЭ-АЛК лечение было прервано из-за сильной боли. Так же в обеих группах примерно у половины пациентов наблюдались эритрема, шелушение и образование поверхностных ран. In 5% of patients in the 5-ALA group and 2% of patients in the MAL group, treatment was interrupted due to severe pain. Also in both groups, approximately half of the patients experienced erythrema, desquamation and the formation of superficial wounds.

achieved in 67-100% of patients. In studies evaluating the recurrence rate, the value was 2-28%, in most studies it was 6-18%.

Interesting comparative data on the efficacy of 5-ALA and MAL were obtained in a study by Alique-García et al. [25]. The authors of the study showed that the efficacy was significantly higher with 5-ALA. Thus, in PDT with 5-ALA, the full effect was obtained in 87% of patients, while in PDT with MAL it was seen only in 76% of patients. The difference in efficacy amounted to 11%. In 12 months after treatment this difference became even greater – 30% (85% vs. 55%). Thus, it can be concluded that the effect after PDT with 5-ALA is maintained longer than after PDT with MAL.

Safety of PDT in Bowen's disease

In most studies, the authors reported painful sensations in patients during irradiation of the pathologic focus [21,22,23]. In rare cases, treatment had to be interrupted due to intolerable pain (from the data by Alique-García et al. [25]: treatment was interrupted in 2-5% of patients). Most authors also point out developing local skin reactions: erythremia, scar formation, hypo- and hyperpigmentation, and desquamation. Most of these adverse events were reversible [24,25].

Number of PDT courses

The number of PDT courses required to achieve a clinically meaningful effect in the treatment of Bowen's disease remains a debated issue. For example, the Scottish PDT Center in Dundee, after performing approximately 5000 PDT treatments in patients with Bowen's disease, estimates incomplete clearance after 4 PDT sessions as a treatment failure. The Center claims that the majority of patients they treated who had complete clearance after PDT achieved it after 2, rarely after 4 sessions [26]. However, there are examples in the literature when patients achieved full recovery after more sessions, for example, 6 [23,27]. Each patient should be individually evaluated on a case-by-case basis when administering PDT [25].

Factors associated with unfavorable prognosis of PDT

In a study by Zaar et al. [24] the following factors associated with poor prognosis in patients with Bowen's disease treated with PDT were identified: large lesion size (> 2 cm) and a single PDT session. In another recent study in which patients with SCSC *in situ* were treated with PDT with 20% 5-ALA solution, it was reported that longer incubation time with 5-ALA, smaller tumor diameter, and facial location were associated with increased efficacy [28]. The dependence of treatment efficacy on the size of the pathologic focus was also confirmed in a study by Morton et al. [7]. Another study showed that severe atypia and older age were associated with an increased risk of treatment failure in PDT of patients with Bowen's disease [29].

Several studies have shown that immunocompromised patients with Bowen's disease had an initial rate of complete effect with PDT was comparable to the main cohort of immunocompetent patients, but a higher rate of recurrence within the first year after treatment was observed in this group [21,30].

Comparative analysis of the efficacy and safety of treatment of Bowen's disease by different methods

An important issue is the comparison of PDT with other treatments for Bowen's disease according to efficacy and safety criteria.

Several direct comparative studies of the efficacy and safety of PDT and other treatments for patients with Bowen's disease have been described in the literature.

A study by Morton et al. [7] showed that cosmetic outcome after 3 months was good or excellent in 94% of patients receiving PDT with MAL, compared with 66% with cryotherapy and 76% with 5-fluorouracil, and was maintained for 12 months.

In the study by Salim et al. [8] it is shown that PDT with 5-ALA in patients with Bowen's disease was accompanied by better clinical results than topical application of 5-fluorouracil: the immediate clinical effect was 88% in the PDT group versus 67% with 5-fluorouracil. After 12 months, complete clinical clearance rates were 82% and 48%, respectively. In addition, PDT demonstrated a better safety profile compared to 5-fluorouracil. With the latter, 7 patients developed severe eczematous reactions, 3 patients developed ulceration and 2 patients developed erosions. No such reactions occurred after PDT.

A meta-analysis performed in 2020 confirmed that PDT is more effective than 5-fluorouracil and cryotherapy for the treatment of Bowen's disease. However, the authors found no significant differences in recurrence rates after treatment with PDT and other treatments (5-fluorouracil and cryotherapy) [9]. In a 2022 meta-analysis of 4 clinical trials involving 292 patients, PDT also showed a higher complete response rate and improved cosmetic results, but also a reduced recurrence rate compared with cryotherapy and 5-fluorouracil [10].

In some studies, the efficacy of PDT was lower than for other topical therapies.

For example, in a study by Park et al. [6] the medical records of 121 patients at Seoul St. Mary's Hospital in Seoul with Bowen's disease were analyzed. The treatment methods were surgical excision, cryotherapy, PDT, and imiquimod. The mean treatment period was longest for cryotherapy, followed by imiquimod, PDT, and surgical excision (119, 88, 68, and 1 day, respectively). The therapeutic efficacy was highest in the surgical removal group (100%) and lowest in the PDT group (62.5%). The recurrence rate was highest in the imiquimod group (33.33%). The authors of the study note that 9% of patients who received cryotherapy developed satellite lesions during the follow-up

period, which requires careful follow-up after treatment of patients with Bowen's disease by cryotherapy [6].

Conclusion

The present data allow us to consider PDT as one of the options for first-line therapy in Bowen's disease. Most studies show that PDT is more effective and safer than 5-fluorouracil and cryotherapy in Bowen's disease [4,5,8,9,10,25]. PDT provides excellent cosmetic results and is generally well tolerated by patients with minimal side effects [17,19,21,22]. The use of PDT is most relevant in patients with Bowen's disease for whom surgery is contraindicated for any reason, patients with multiple lesions [17], foci located on the lower extremities [25] and with recurrent Bowen's disease [17].

Although there are many different PDT protocols for Bowen's disease, most studies perform 2 courses of PDT 7 days apart using red light (≈ 630 nm) at a dose of approximately 37 J/cm^2 after application of 5-ALA or MAL under occlusion for 3-4 h to obtain optimal results [20,22,24,25].

REFERENCES

1. Clinical recommendations of the Russian Federation 2020 «Squamous cell skin cancer».
2. Sharma A. et al. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma in situ (Bowen disease) 2022. *British Journal of Dermatology*, 2023, vol. 188(2), pp. 186-194.
3. Namgoong S. et al. Association of human papillomavirus and extra-genital Bowen disease (squamous cell carcinoma in situ): a systematic review, *Journal of the American Academy of Dermatology*, 2021, vol. 84(3), pp. 822-825.
4. O'Connell K.A., Okhovat J.P., Zeitouni N.C. Photodynamic therapy for Bowen's Disease (squamous cell carcinoma in situ) current review and update, *Photodiagnosis and photodynamic therapy*, 2018, vol. 24, pp. 109-114
5. Khismatullina Z.R. et al. Bowen's disease (literature review), *Creative surgery and*, 2023, vol. 13(1), pp. 68-76.
6. Park H.E. et al. Analysis on the effectiveness and characteristics of treatment modalities for Bowen's disease: An observational study, *Journal of Clinical Medicine*, 2022, vol. 11(10), pp. 2741.
7. Morton C. et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial, *Archives of dermatology*, 2006, vol. 142(6), pp. 729-735.
8. Salim A. et al. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease, *British Journal of Dermatology*, 2003, vol. 148(3), pp. 539-543.
9. Zhong S. et al. Efficacy of photodynamic therapy for the treatment of Bowen's disease: An updated systematic review and meta-analysis of randomized controlled trials, *Photodiagnosis and Photodynamic Therapy,* 2020, vol. 32. p. 102037.
10. Xue W. L. et al. Efficacy of Photodynamic Therapy for the Treatment of Bowen's Disease: A Meta-Analysis of Randomized Controlled Trials, *Dermatology*, 2022, vol. 238(3), pp. 542-550.
11. Ivanova-Radkevich V. I. Biochemical Basis of Selective Accumulation and Targeted Delivery of Photosensitizers to Tumor Tissues, *Biochemistry (Moscow),* 2022, vol. 87(11), pp. 1226-1242
12. Reshetov I.V., Korenev S.V., Romanko Yu.S. Modern aspects of photodynamic therapy of basal cell skin cancer, *Biomedical Photonics*, 2022, vol. 11(3), pp. 35-39. doi: 10.24931/2413–9432–2022–11-3-35–39
13. Filonenko E.V., Okushko S.S. Actinic keratosis (review of literature), *Biomedical Photonics*, 2022, vol. 11(1), pp. 37-48. doi: 10.24931/2413–9432–2022–11-1-37-48.
14. Kaprin A.D., Ivanova-Radkevich V.I., Urlova A.N., Asratov A.T., Gushchina Yu.,Sh., Libo L., Xiaojun C., Filonenko E.V. Photodynamic therapy opportunities for the treatment of erythroplasia of Queyrat, *Biomedical Photonics*, 2020, vol. 9(1), pp. 34-41. (in Russian) doi: 10.24931/2413–9432–2020–9-1–34–41

ЛИТЕРАТУРА

1. Клинические рекомендации РФ 2020 «Плоскоклеточный рак кожи»
2. Sharma A. et al. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma in situ (Bowen disease) 2022 // British Journal of Dermatology. – 2023. – Vol. 188(2). – P. 186-194.
3. Namgoong S. et al. Association of human papillomavirus and extra-genital Bowen disease (squamous cell carcinoma in situ): a systematic review // Journal of the American Academy of Dermatology. – 2021. – Vol. 84(3). – P. 822-825.
4. O'Connell K.A., Okhovat J.P., Zeitouni N.C. Photodynamic therapy for Bowen's Disease (squamous cell carcinoma in situ) current review and update // Photodiagnosis and photodynamic therapy. – 2018. – Vol. 24. – P. 109-114
5. Хисматуллина З.Р. и др. Болезнь Боуэна (обзор литературы) // Креативная хирургия и онкология. – 2023. – Т. 13, №. 1. – С. 68-76.
6. Park H.E. et al. Analysis on the effectiveness and characteristics of treatment modalities for Bowen's disease: An observational study // Journal of Clinical Medicine. – 2022. – Vol. 11(10). – P. 2741.
7. Morton C. et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial //Archives of dermatology. – 2006. – Vol. 142(6). – P. 729-735.
8. Salim A. et al. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease // British Journal of Dermatology. – 2003. – Vol. 148(3). – P. 539-543.
9. Zhong S. et al. Efficacy of photodynamic therapy for the treatment of Bowen's disease: An updated systematic review and meta-analysis of randomized controlled trials // Photodiagnosis and Photodynamic Therapy. – 2020. – Vol. 32. – P. 102037.
10. Xue W. L. et al. Efficacy of Photodynamic Therapy for the Treatment of Bowen's Disease: A Meta-Analysis of Randomized Controlled Trials // Dermatology. – 2022. – Vol. 238(3). – P. 542-550.
11. Ivanova-Radkevich V. I. Biochemical Basis of Selective Accumulation and Targeted Delivery of Photosensitizers to Tumor Tissues // Biochemistry (Moscow). – 2022. – Vol. 87(11). – P. 1226-1242
12. Reshetov I.V., Korenev S.V., Romanko Yu.S. Modern aspects of photodynamic therapy of basal cell skin cancer // Biomedical Photonics. – 2022. – Vol. 11(3). – P. 35-39. doi: 10.24931/2413–9432–2022–11-3-35–39
13. Filonenko E.V., Okushko S.S. Actinic keratosis (review of literature) // Biomedical Photonics. – 2022. – Vol. 11(1). – P. 37-48. doi: 10.24931/2413–9432–2022–11-1-37-48.
14. Kaprin A.D., Ivanova-Radkevich V.I., Urlova A.N., Asratov A.T., Gushchina Yu.,Sh., Libo L., Xiaojun C., Filonenko E.V. Photodynamic therapy opportunities for the treatment of erythroplasia of Queyrat // Biomedical Photonics. – 2020. – Vol. 9(1). – P. 34-41. (in Russian) doi: 10.24931/2413–9432–2020–9-1–34–41

15. Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy in the treatment of extramammary Paget disease, *Biomedical Photonics*, 2022, vol. 11(3), pp. 24-34. doi: 10.24931/2413–9432–2022–11-3-24–34.
16. Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy in the treatment of patients with mycosis fungoides, *Biomedical Photonics*, 2022, vol. 11(1), pp. 27-36. doi: 10.24931/2413–9432–2022–11-1-27-37
17. Zeitouni N.C. et al. Photodynamic therapy with 5-aminolevulinic acid 10% gel and red light for the treatment of actinic keratosis, nonmelanoma skin cancers, and acne: Current evidence and best practices, *The Journal of Clinical and Aesthetic Dermatology*, 2021, vol. 14(10), p. E53.
18. Varma S. et al. Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large-field incoherent light source, *British Journal of Dermatology*, 2001, vol. 144(3), pp. 567-574.
19. de Haas E. R. M. et al. Response of Bowen disease to ALA-PDT using a single and a 2-fold illumination scheme, *Archives of dermatology*, 2007, vol. 143(2), pp. 264-276.
20. Calzavara-Pinton P.G. et al. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma, *British Journal of Dermatology*, 2008, vol. 159(1), pp. 137-144.
21. Cavicchini S. et al. Long-term follow-up of metil aminolevulinate (MAL)-PDT in difficult-to-treat cutaneous Bowen's disease, *International journal of dermatology*, 2011, vol. 50(8), pp. 1002-1005.
22. Truchuelo M. et al. Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions, *Journal of the European Academy of Dermatology and Venereology*, 2012, vol. 26(7), pp. 868-874.
23. Ratour-Bigot C. et al. Squamous cell carcinoma following photodynamic therapy for cutaneous Bowen's disease in a series of 105 patients, *Acta dermato-venereologica*, 2016, vol. 96(5), pp. 658-663.
24. Zaar O. et al. Effectiveness of photodynamic therapy in Bowen's disease: a retrospective observational study in 423 lesions, *Journal of the European Academy of Dermatology and Venereology*, 2017, vol. 31(8), pp. 1289-1294.
25. Alique-García S. et al. Treatment of Bowen's disease with photodynamic therapy. Observational study in 171 patients with 5-aminolaevulinic acid (BF-200 ALA) and methyl aminolaevulinate (MAL), *Photodiagnosis and Photodynamic Therapy*, 2019, vol. 28, pp. 192-194.
26. Attili S. K., Ibbotson S. H. How we treat Bowen's disease with topical photodynamic therapy in Dundee, *Photodiagnosis and photodynamic therapy*, 2009, vol. 6(1), pp. 41-45.
27. Kang H. K. et al. Photodynamic therapy for Bowen's disease of the vulva area, *Annals of Dermatology*, 2014, vol. 26(2), pp. 241-245.
28. Kibbi N. et al. Photodynamic therapy for cutaneous squamous cell carcinoma in situ: Impact of anatomic location, tumor diameter, and incubation time on effectiveness, *Journal of the American Academy of Dermatology,* 2020, vol. 82(5), pp. 1124-1130.
29. Westers-Attema A. et al. Photodynamic therapy in Bowen's disease: influence of histological features and clinical characteristics on its success, *Dermatology*, 2015, vol. 230(1), pp. 55-61.
30. Dragieva G. et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients, *Transplantation*, 2004, vol. 77(1), pp. 115-121.

15. Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy in the treatment of extramammary Paget disease // Biomedical Photonics. – 2022. – Vol. 11(3). – P. 24-34. doi: 10.24931/2413–9432–2022–11-3-24–34.
16. Filonenko E.V., Ivanova-Radkevich V.I. Photodynamic therapy in the treatment of patients with mycosis fungoides // Biomedical Photonics. – 2022. – Vol. 11(1). – P. 27-36. doi: 10.24931/2413–9432–2022–11-1-27-37
17. Zeitouni N.C. et al. Photodynamic therapy with 5-aminolevulinic acid 10% gel and red light for the treatment of actinic keratosis, nonmelanoma skin cancers, and acne: Current evidence and best practices // The Journal of Clinical and Aesthetic Dermatology. – 2021. – Vol. 14(10). – P. E53.
18. Varma S. et al. Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large-field incoherent light source // British Journal of Dermatology. – 2001. – Vol. 144(3). – P. 567-574.
19. de Haas E. R. M. et al. Response of Bowen disease to ALA-PDT using a single and a 2-fold illumination scheme //Archives of dermatology. – 2007. – Vol. 143(2). – P. 264-276.
20. Calzavara-Pinton P.G. et al. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma // British Journal of Dermatology. – 2008. – Vol. 159(1). – P. 137-144.
21. Cavicchini S. et al. Long-term follow-up of metil aminolevulinate (MAL)-PDT in difficult-to-treat cutaneous Bowen's disease // International journal of dermatology. – 2011. – Vol. 50(8). – P. 1002-1005.
22. Truchuelo M. et al. Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions //Journal of the European Academy of Dermatology and Venereology. – 2012. – Vol. 26(7). – P. 868-874.
23. Ratour-Bigot C. et al. Squamous cell carcinoma following photodynamic therapy for cutaneous Bowen's disease in a series of 105 patients //Acta dermato-venereologica. – 2016. – Vol. 96(5). – P. 658-663.
24. Zaar O. et al. Effectiveness of photodynamic therapy in Bowen's disease: a retrospective observational study in 423 lesions // Journal of the European Academy of Dermatology and Venereology. – 2017. – Vol. 31(8). – P. 1289-1294.
25. Alique-García S. et al. Treatment of Bowen's disease with photodynamic therapy. Observational study in 171 patients with 5-aminolaevulinic acid (BF-200 ALA) and methyl aminolaevulinate (MAL) // Photodiagnosis and Photodynamic Therapy. – 2019. – Vol. 28. – P. 192-194.
26. Attili S. K., Ibbotson S. H. How we treat Bowen's disease with topical photodynamic therapy in Dundee // Photodiagnosis and photodynamic therapy. – 2009. – Vol. 6(1). – P. 41-45.
27. Kang H. K. et al. Photodynamic therapy for Bowen's disease of the vulva area //Annals of Dermatology. – 2014. – Vol. 26(2). – P. 241-245.
28. Kibbi N. et al. Photodynamic therapy for cutaneous squamous cell carcinoma in situ: Impact of anatomic location, tumor diameter, and incubation time on effectiveness // Journal of the American Academy of Dermatology. – 2020. – Vol. 82(5). – P. 1124-1130.
29. Westers-Attema A. et al. Photodynamic therapy in Bowen's disease: influence of histological features and clinical characteristics on its success // Dermatology. – 2015. – Vol. 230(1). – P. 55-61.
30. Dragieva G. et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients // Transplantation. – 2004. – Vol. 77(1). – P. 115-121.

CASE REPORTS

PHOTODYNAMIC THERAPY FOR A PATIENT WITH BASAL CELL SKIN CANCER OF THE LOWER EYELID (CLINICAL CASE)

Filonenko E.V., Grigoryevykh N.I.
P.A. Herzen Moscow Oncology Research Center – branch of FSBI NMRRC of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract

The article provides an example of successful treatment of a patient with basal cell skin cancer of the lower eyelid of the right eye, stage IB cT2aN0M0, with the presence of concomitant pathology – a decrease in the activity of plasma factor XII of blood coagulation (Hageman disease). The patient's medical history is associated with long-term ineffective treatment of the tumor with Curaderm ointment. After diagnosis and further examination at the Moscow Research Institute named after. P.A. Herzen, at the Center for Laser and Photodynamic Diagnostics and Therapy of Tumors, the patient underwent organ-preserving treatment using photodynamic therapy. 1 course of photodynamic therapy with the photosensitizer chlorin e6 was carried out. Complete tumor regression was obtained; relapse-free follow-up period was 1 year.

Key words: basal cell skin cancer, photodynamic therapy, photosensitizer.

Contacts: Filonenko E.V., e-mail: elena.filonenko@list.ru

For citations: Filonenko E.V., Grigoryevykh N.I. Photodynamic therapy for a patient with basal cell skin cancer of the lower eyelid (clinical case), *Biomedical Photonics*, 2023, vol. 12, no. 4, pp. 30–32. doi: 10.24931/2413–9432–2023–12-4-30–32.

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ БОЛЬНОЙ БАЗАЛЬНОКЛЕТОЧНЫМ РАКОМ КОЖИ НИЖНЕГО ВЕКА (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

Е.В. Филоненко, Н.И. Григорьевых
«Московский научно-исследовательский онкологический институт им. П.А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации, Москва, Россия

Резюме

В статье приведен пример успешного лечения больной базальноклеточным раком кожи нижнего века правого глаза IБ стадии cT2aN0M0 с наличием сопутствующей патологии – снижение активности плазменного фактора XII свертывания крови (болезнь Хагемана). Анамнез заболевания пациентки связан с длительным неэффективным лечением опухоли мазью курадерм. После постановки диагноза и дообследования в МНИОИ им. П.А. Герцена, в Центре лазерной и фотодинамической диагностики и терапии опухолей пациентке проведено органосохраняющее лечение методом фотодинамической терапии. Проведен 1 курс фотодинамической терапии с фотосенсибилизатором хлорин е6. Получена полная регрессия опухоли, срок безрецидивного наблюдения – 1 год.

Ключевые слова: базальноклеточный рак кожи, фотодинамическая терапия, фотосенсибилизатор.

Контакты: Филоненко Е.В., e-mail: elena.filonenko@list.ru

Для цитирования: Филоненко Е.В., Григорьевых Н.И. Фотодинамическая терапия больной базальноклеточным раком кожи нижнего века (клиническое наблюдение) // Biomedical Photonics. – 2023. – Т. 12, № 4. – С. 30–32.. doi: 10.24931/2413–9432–2023–12-4-30–32.

Basal cell skin cancer (BCSC or basal cell carcinoma (BCC)) is one of the most common tumors in Russia. In the Russian Federation, the incidence of skin cancer ranks first (both sexes) among all malignant neoplasms. In men it ranks third after lung and prostate cancer. In women it is second only to breast cancer. According to statistical data, in 2022, the prevalence of malignant tumors of the skin (except melanoma) in the Russian

population was 298.9 per 100 thousand population, which is 18.47% higher than the level in 2012 (252.3). In Russia, 584,061 all cancers were registered in 2022, of which skin cancers (except melanoma) accounted for 79,124 patients. In 2022, skin cancers (except melanoma) were registered in stages I–II in 96.8% of cases, in stage III – in 2.3%, stage IV – in 0.6% [1].

According to the literature, BCC is most often localized on the skin of the head and neck [2]. According to a 27-year retrospective review of 5,755 cases of BCC, tumors were more common in high-risk areas (central face, eyebrows, nose, lips, chin, ear, temporal areas) and were greater than or equal to 6 mm in diameter, and tumors in moderate risk areas (cheeks, forehead, scalp, neck, jawline, lower leg) were greater than or equal to 10 mm in diameter. BCC in the head and neck region, including the "H zone" or "mask zone" of the face, has a higher risk and propensity for recurrence than those developing in the trunk and extremities [3].

According to the clinical recommendations of the Association of Oncologists of Russia, for the treatment of patients with BCC of the central zone of the face, it is recommended for all patients with an established diagnosis of low risk, where surgery and radiation for any reason are contraindicated or inappropriate, or the patient refuses due to dissatisfaction with the expected cosmetic results, or due to the general condition of the patient, etc., it is recommended to carry out any of the destructive treatment methods: curettage, electrocoagulation, cryodestruction, photodynamic therapy (PDT) or use topical agents with antitumor activity. All patients diagnosed with high-risk BCC are recommended to undergo tumor removal with intraoperative monitoring of all (peripheral and deep) resection margins during a pathological and anatomical examination of the surgical material [4].

Clinical recommendations of the NCCN regulate the use of curettage and electrodissection, surgery, radiation treatment, PDT, imiquimod, and cryotherapy for the treatment of patients with an established diagnosis of BCC of the central zone of the face at low risk in this localization. For patients diagnosed with high-risk BCC, surgical treatment is recommended; for inoperable patients, radiation therapy is recommended [5].

In recent decades, significant clinical material has been accumulated indicating the effectiveness of PDT regardless of tumor location [6].

Clinical case

We present a clinical observation. Patient A., born in 1983, in 2015 noted the appearance of a formation in the form of a pimple in the skin of the lower eyelid of the right eye. In 2016, the patient went to the skin and venereal disease clinic at the place of residence, where a cytological examination of scrapings from the formation was performed and BCC was verified. The patient was sent to the oncology clinic at the place of residence. Radiation treatment was offered, which the patient refused.

Next, the patient contacted the Federal State Budgetary Institution "National Medical Research Center of Oncology named after. N.N. Blokhin" of the Russian Ministry of Health, where therapy with Curaderm ointment was prescribed and lasted more than a year. During treatment, the tumor continued to grow. In June 2022, the patient contacted the Federal State Autonomous Educational Institution of Higher Education "First Moscow State Medical University named after. I.M. Sechenov" of the Ministry of Health of Russia, where a biopsy was performed on July 21, 2022 and the diagnosis of BCC was confirmed.

In August 2022, the patient independently contacted the P.A. Herzen Moscow Oncology Research Center, glass slides were reviewed, the diagnosis was confirmed (No. 22/1-01533 – BCC of glandular-cystic structure). Upon presentation, a tumor formation was detected on the skin of the lower eyelid of the right eye, spreading to the ciliary edge of the eyelid, with a maximum size of up to 1.7 cm in the form of an infiltrate with an exophytic component and cicatricial changes in the center.

According to ultrasound data of a tumor of the skin of the lower eyelid on the right and the lymph nodes of the neck: in the projection of the detected changes in the skin of the eyelid, a formation is visualized, rising above the surface of the skin, of a hypoechoic homogeneous structure, with smooth, clear contours, moderately vascularized, measuring about 5.5x2.5x4 mm, where 2.5 mm is the thickness, and the contour of the basal layer can be clearly traced – no obvious signs of invasion have been identified behind it.

The thickness of the skin outside the formation is about 1.2 mm. On the neck on both sides, including the submandibular, pre- and paratracheal, supraclavicular areas, along the main vascular bundles and along the posterolateral surfaces of the neck, pathologically changed and enlarged lymph nodes and additional pathological formations are not visualized. Final report: echography of skin formation of the lower eyelid on the right is without signs of invasion beyond the basal layer and without signs of atypical changes in the lymph nodes of the neck.

The clinical situation was discussed at an extended consultation, where the patient was recommended for surgical treatment, and was hospitalized in the microsurgical department. During the preoperative examination, deviations in the hemostatic system were revealed: aPTT was outside the measurement range, lupus anticoagulant was outside the measurement range.

Due to pronounced hypocoagulation according to laboratory tests, surgical intervention was not performed, the patient was sent for further examination in

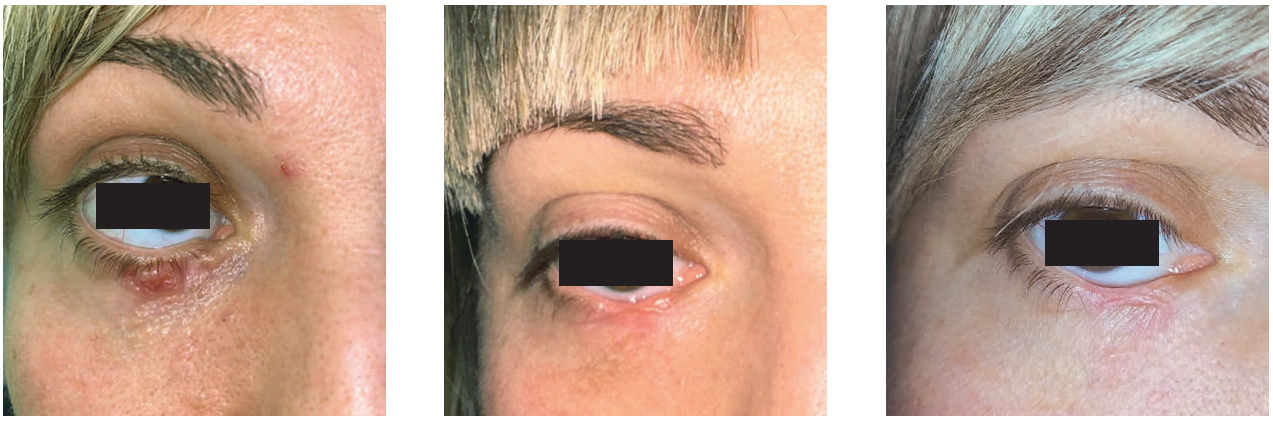


Рис. Фото нижнего века больной А.: a – опухоль до ФДТ; b – рубец в зоне опухоли через 6 мес после ФДТ; c – рубец в зоне опухоли через 1 год после ФДТ.
Fig. Photo of the lower eyelid of patient A.: a – tumor before PDT; b – scar in the tumor area 6 months after PDT; c – scar in the tumor area 1 year after PDT.

order to identify the genesis of the blood clotting disorder. The patient was consulted at the Federal State Budgetary Institution "National Medical Research Center for Hematology" of the Ministry of Health of Russia; additional examination revealed a decrease in the activity of plasma factor XII of blood coagulation (Hageman's disease), and a plan for a follow-up examination was drawn up for 12 weeks.

Patient at the P.A. Herzen Moscow Oncology Research Center was re-discussed at the council: taking into account the concomitant pathology of the hemostatic system (Hageman's disease, deficiency of the 12th clotting factor), which requires a lengthy clarifying examination, the localization and nature of tumor growth. The patient was recommended to undergo PDT.

On November 10, 2022 PDT course was completed (Fig.). The patient tolerated the treatment satisfactorily, there were no complications. The patient was observed for a year without relapse with a good cosmetic result.

This clinical observation demonstrates the effectiveness of the PDT method in the treatment of stage cT2aN0M0 BCC localized in the skin of the eyelids. Despite the presence of concomitant pathology associated with severe hypocoagulation and the spread of tumor infiltration to the ciliated edge of the eyelid, the treatment was carried out without complications; after PDT, not only complete tumor removal was obtained, but also a good cosmetic effect.

REFERENCES

1. Sostoyanie onkologicheskoi pomoshchi naseleniyu v Rossii v 2022 godu. Ed by Kaprin A.D., Starinskii V.V., Shakhzadova A.O. Moscow: 2023. (In Russ).
2. Petrovich Z., Kuisk H., Langholz B., et al. Treatment results and patterns of failure in 646 patients with carcinoma of the eyelids, pinna, and nose. *Am J Surg*, 1987, vol. 154, pp. 447-450.
3. Silverman M.K., Kopf A.W., Grin C.M., et al. Recurrence rates of treated basal cell carcinomas. Part 1: Overview. *J Dermatol Surg Oncol*, 1991, vol. 17, pp. 713-718.
4. Clinical recommendations of the AOR for the treatment of basal cell carcinoma of the skin. Moscow 2020.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Basal Cell Skin Cancer Version* 2.2024 — September 14, 2023.
6. Filonenko E.V. The history of development of fluorescence diagnosis and photodynamic therapy and their capabilities in oncology. *Russian Journal of General Chemistry*, 2015, vol. 85(1), pp. 211-216.

ЛИТЕРАТУРА

1. Состояние онкологической помощи населению России в 2022 году под редакцией А.Д. Каприна, В.В. Старинского, А.О. Шахзадовой, Москва 2023г.
2. Petrovich Z., Kuisk H., Langholz B., et al. Treatment results and patterns of failure in 646 patients with carcinoma of the eyelids, pinna, and nose // Am J Surg. – 1987. – Vol. 154. – P. 447-450.
3. Silverman M.K., Kopf A.W., Grin C.M., et al. Recurrence rates of treated basal cell carcinomas // Part 1: Overview. J Dermatol Surg Oncol. – 1991. – Vol. 17. – P. 713-718.
4. Клинические рекомендации АОР по лечению базальноклеточного рака кожи. Москва 2020 г.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) // Basal Cell Skin Cancer Version 2.2024 — September 14, 2023.
6. Filonenko E. V. The history of development of fluorescence diagnosis and photodynamic therapy and their capabilities in oncology // Russian Journal of General Chemistry. – 2015. – Vol. 85(1). – P. 211-216.

ЖИВАЯ
ЭНЕРГИЯ
СВЕТА

Фоторан e6®

НОВЫЙ РОССИЙСКИЙ ПРЕПАРАТ ДЛЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ

- Действующее вещество природного происхождения
- Отсутствие аллергических реакций
- Отсутствие гепато и нефротоксичности, низкая фототоксичность
- Быстрое накопление в патологической ткани – 1,5-3 часа
- Длительное хранение без потери активности вещества – 3 года
- Низкая стоимость

ПАРТНЁРЫ:

Московский Научно-Исследовательский Онкологический Институт им. П.А.Герцена

Национальный медицинский исследовательский центр онкологии

Адыгейский республиканский онкологический диспансер

СККОД

ГБУЗ Челябинский областной клинический центр онкологии и ядерной медицины

По вопросам приобретения

+7 (495) 659-64-93
+7 (499) 726-26-98

ФОТОСЕНСИБИЛИЗАТОРЫ НОВОГО ПОКОЛЕНИЯ ДЛЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ

«ФОТОДИТАЗИН®» концентрат для приготовления раствора для инфузий — лекарственное средство (РУ № ЛС 001246 от 18.05.2012 г.)
«ФОТОДИТАЗИН®» гель — изделие медицинского назначения (РУ № ФСР 2012/13043 от 03.02.2012 г.)
«ФОТОДИТАГЕЛЬ®» — косметическое средство (ДС ЕАЭС № RU Д-RU.НВ42.В.06108/20 от 24.09.2020 г.)

Препараты применяются для флюоресцентной диагностики и фотодинамической терапии злокачественных новообразований, а так же патологий не онкологического характера в следующих областях медицины:

- гинекология
- урология
- нейрохирургия
- торакальная хирургия
- офтальмология
- травматология
- ортопедия
- комбустиология
- гнойная хирургия
- дерматология
- косметология
- стоматология

www.fotoditazin.com
www.фотодитазин.рф

@FOTODITAZIN

@FOTODITAGEL_FDT

ООО «ВЕТА-ГРАНД»
123056, г. Москва, ул. Красина, д. 27, стр. 2
Тел.: +7 (499) 250-40-00, +7 (929) 971-44-46
E-mail: veta-grand@mail.ru