FLUORESCENT DIAGNOSTICS OF NON-MELANOMA SKIN CANCER

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Abstract

Fluorescent diagnostics is a promising method for diagnosing non-melanocytic skin tumors, which makes it possible to identify clinically undetectable skin cancer foci and clarify the margin of the tumor lesion. The main drugs for fluorescent diagnostics are drugs based on 5-aminolevulinic acid and its methyl ester. Sensitivity indicators of fluorescent diagnostics in basal cell, squamous cell carcinoma and extramammary Paget's disease reach 79.0-100.0%, specificity – 55.6-100%. But the effectiveness of this method may be reduced due to hyperkeratinization, keratinization, and the presence of necrotic tissue on the surface of tumor foci. Comparative studies of the results of fluorescent diagnostics and histological mapping during tumor removal using Mohs micrographic surgery showed approximately equal results in the determining of the tumor edges by these methods, which indicates that safe and technically easily performed fluorescent diagnostics can serve as a good alternative to Mohs micrographic surgery, one of the most accurate, but rather labor-intensive and technically complex method for determining the margin of skin cancer foci.

Key words: fluorescent diagnostics, skin cancer, basal cell carcinoma, squamous cell carcinoma, Paget's extramammary desease, tumor margin, 5-aminolevulinic acid, 5-aminolevulinic acid methyl ester.

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ФЛУОРЕСЦЕНТНАЯ ДИАГНОСТИКА ПРИ НЕМЕЛАНОЦИТАРНЫХ ОПУХОЛЯХ КОЖИ

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Резюме

Флуоресцентная диагностика – перспективный метод диагностики немеланоцитарных опухолей кожи, который позволяет выявить клинически не определяемые очаги рака кожи и уточнить границы распространения опухолевого процесса. Основными лекарственным препаратами для проведения флуоресцентной диагностики являются лекарства на основе 5-аминолевулиновой кислоты и ее метилового эфира. Показатели чувствительности флуоресцентной диагностики при базальноклеточном, плоскоклеточном раке кожи и экстрамаммарном раке Педжета достигают 79,0-100,0%, специфичности – 55,6-100%. Эффективность этого метода может снижаться за счет гиперкератинизации, ороговения и присутствия некротической ткани на поверхности опухолевых очагов. Сравнительные исследования результатов флуоресцентной диагностики и гистологического картирования при удалении опухоли методом микрографической хирургии Мооса показали высокую корреляцию результатов определения краев опухоли этими методами, что свидетельствует о том, что безопасная и технически легко выполнимая флуоресцентная диагностика может служить хорошей альтернативой микрографической хирургии Мооса – одному из наиболее точных, но достаточно трудозатратному и технически сложному методу определения границ очагов рака кожи.

Ключевые слова: флуоресцентная диагностика, рак кожи, базальноклеточный рак кожи, плоскоклеточный рак кожи, экстрамаммарный рак Педжета, край опухоли, 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты.

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Introduction

Tumor lesions of the skin are one of the most common neoplasms in the structure of oncological morbidity. In recent decades, there has been a significant increase in the incidence of skin cancer in the world. In 2021, 68,240 cases of skin cancer (except for melanoma) were detected in Russia, and 442 619 patients diagnosed with skin cancer (except for melanoma) were under dispensary registration by the end of 2021 [1]. Successful treatment of patients with malignant skin tumors is based on the implementation of adequate specialized treatment, which is ensured only by timely and accurate diagnosis with an assessment of the exact margin of the tumor lesion. Diagnosis of tumors and precancerous lesions of the skin is based on the data of the clinical picture obtained during a visual external examination of the patient, and instrumental research methods. To detect skin cancer, fluorescence diagnostics (FD) is successfully used – a study based on the selective accumulation of a photosensitizer or the induction of the formation of endogenous photosensitizers – porphyrins – in the tumor tissue, followed by registration of their fluorescence when irradiated with light of a certain wavelength [2,3].

There are few works devoted to the use of FD as a diagnostic method in clinical practice. A search in the Pubmed database for the keywords "fluorescent diagnostics, photodiagnostics, photodynamic diagnostics, photosensitizer, skin tumors" revealed about 150 scientific papers, 80% of which were devoted to studying the kinetics of photosensitizer accumulation in tumor foci and healthy skin using local fluorescence spectroscopy for optimization methods of photodynamic therapy with various photosensitizers, as well as the study of the phenomenon of autofluorescence of tumor tissues. Only 19 articles over the past 20 years have been relevant to the subject of this review. The data presented in them was analyzed and included in the review.

In most studies, 5-aminolevulinic acid (5-ALA) and its derivatives are used to perform fluorescent diagnosis of non-melanocytic skin tumors. 5-ALA is an intermediate metabolite in heme biosynthesis. Exogenous administration of 5-ALA increases the rate of production of photoactive protoporphyrin IX (PPIX) in all cells of the body in which the process of heme biosynthesis occurs. The enzyme ferrochelatase catalyzes the conversion of PPIX to photoinactive heme. In unaltered cells, this process occurs rather quickly (2–4 h). In tumor cells, due to the higher activity of the enzymes of the initial stage of heme synthesis (in particular, porphobilinogen deaminase), as well as a decrease in the activity in them of ferrochelatase (due to the limited availability of Fe^{2+}), photoactive PPIX accumulates. An increase in the concentration of PPIX in the tumor occurs within a few hours, and its high level is maintained for up to 24 hours, while in normal cells PPIX is quickly converted into photoinactive heme under the action of ferrochelatase. Thus, in the interval from approximately 2 to 24 hours, there is a significant difference (up to 10–15 times) between the concentration of photoactive PPIX in tumor and healthy tissues. This makes it possible to perform the PDT procedure with minimal impact on healthy tissues, to determine the optimal resection margins during surgical removal, and to perform highly efficient fluorescent diagnostics to detect tumors and clarify their margin [2,4,5].

It should be noted that even without exogenous administration of 5-ALA in tissues of locally advanced, especially decaying tumors, the fluorescence of porphyrins is slightly higher than in surrounding healthy tissues due to the biochemical mechanisms described above. C.T. Andrade et al. consider that only additional exogenous administration of 5-ALA and its derivatives in most cases leads to an increase in the fluorescence contrast of tumor and healthy tissues and the possibility of a complete diagnosis [6]. In their studies, these authors demonstrated intense autofluorescence in foci of basal cell carcinoma (BCC), actinic keratosis, and, to a lesser extent, seborrheic keratosis. For actinic keratosis and seborrheic keratosis foci, additional application of topical 5-ALA solution did not lead to an increase in fluorescence intensity. The authors believe that a possible cause was the inefficient penetration of the 5-ALA solution due to hyperkeratinization and necrotic tissue on the surface of the lesions. Also, part of the lesions of BCC and actinic keratosis had extensive keratinization on the surface, which apparently acted as a physical barrier to the penetration of the 5-ALA solution. In such foci, even 60 min after the application of 5-ALA, no increase in fluorescence intensity was noted. A possible solution is to remove the keratin layer by curettage, which is a simple medical procedure. For SC foci, high light absorption by melanin prevents fluorescence visualization both in the case of autofluorescence and in fluorescent diagnostics with exogenous administration of 5-ALA. The fluorescence intensity of BCC foci significantly increased after topical application of a 5-ALA solution, which allowed the authors to recommend FD for the diagnosis of this pathology.

In the study by S. Neus et al. [7] also confirmed the high diagnostic value of FD in patients with BCC. The authors evaluated the effectiveness of FD in patients with foci of BCC on the scalp. Tumor margin were determined using a Wood's lamp by fluorescence after exposure to 20% 5-ALA ointment for 3.5 hours. Tumor resection was performed along the margin determined using FD. 28 foci of BCC were analyzed. In 22 (78.6%) cases, the margin determined by FD completely coincided with the results of histopathological examination. In 6 foci, the margin determined by FD did not correlate with the histopathologically assessed tumor margin. Of these,

4 (14.3%) lesions were not completely removed; Two (7.1%) lesions were completely resected, indicating that the tumor was within the FD-defined margin, but not at the resection margin. Therefore, the rate of incomplete removal of BCC lesions was 14.3% (4/28). FD sensitivity and specificity were 79% and 100%, respectively.

In 2015 E.V. Filonenko [2] published the results of a study on the efficacy of FD with 5-ALA (oral solution at a dose of 1.0 mg/kg 3 hours before diagnosis) in 237 patients with BCC, squamous cell carcinoma (SCC) and metatypical skin cancer. In 100% of patients, FD made it possible to clarify the margin of tumor foci. In 118 patients, 506 foci of additional fluorescence were detected, of which 63 patients were diagnosed with skin cancer during morphological examination. The sensitivity of the method was 100.0%, the specificity was 55.6%

Similar results were obtained in other studies of FD in patients with BCC and SCC. So, in the study of J. Liutkeviciute-Navickiene et al. [8] FD with 5-ALA and 5-ALA methyl ester (MAL) as a topical application was performed in 126 patients with CCCC and SCC. The sensitivity of the method was 95.4%, the specificity was 88.6%. In the work of Y. Won et al. [9] FD with ME-5ALA using computerized analysis of fluorescent images was performed in 10 patients with BCC. The sensitivity of the method was 82.6%, the specificity was 94.1%.

In recent years, the number of studies has been published in which the effectiveness of FD with 5-ALA and its derivatives was evaluated in comparison with Mohs micrographic surgery (MMS), one of the most accurate, but rather labor-intensive and technically complex method for determining the margin of skin cancer foci. When using MMS, the neoplasm is excised with simultaneous histological examination of layered sections. The affected tissue is removed layer by layer, and the removed layers are sent for urgent histological analysis. If malignant cells are found in it, tissue excision continues. This happens until the entire next resected area consists of healthy tissues. MMS provides intraoperative microscopic assessment of 100% of the lesion margins, which allows the removal of only the affected tissue and reduces the recurrence rate [10]. The high prevalence of skin cancer, combined with the costs and time associated with MMS, determines the relevance of developing new methods for refining tumor margins that could increase the effectiveness of MMS or serve as an alternative to MMS [11,12]. These studies have shown a correlation between the results of determining the edges of the tumor by the FD method with the results of determining the edges of the tumor by the MMS method.

In the study by B. Stenquist et al. [13] in 12 patients with basal cell skin cancer (BCC), fluorescence after application of 5-ALA ointment and histological mapping using MMS correlated in 42% of tumors with partial correlation in other lesions. A.M. Wennberg et al. [14] showed a strong correlation of tumor margins on digital fluorescence imaging after pre-exposure of 5-ALA ointment with MMS histological mapping in 50% of patients. Another study [15] evaluated the effectiveness of using FD with MAL to clarify the margin of the tumor lesion of BCC foci. The exposure time of the ointment with a photosensitizer was increased compared to standard methods and averaged 13 hours. The study involved 27 patients with BCC with lesions with an average diameter of 1.05 ± 0.35 cm. The margin of tumor foci was determined using a digital fluorescence imaging system with assessment of PPIX accumulation in tumor tissue relative to normal tissue. The BCC lesions were then surgically removed according to defined margins using MMS. In 12 (44.44%) of 27 foci, the edge of the tumor, according to FD, coincided with the histopathological picture. The average fluorescent contrast value was 2.7. Although 15 pigmented BCC lesions showed reduced or absent fluorescence in the center, fluorescence in their periphery was used as a guide for resection. In these 15 lesions, the number of additional MMS resection steps required to clear the lateral margin, each with an additional 1 mm excision, was one step in 14 (93.3%) BCC lesions and two steps in 1 (6.6%) BCC lesion. Results similar in effectiveness were obtained in a study by Jeon et al. [sixteen]. In 38 patients with SCC, the margin of the tumor was determined by the FD method with 5-ALA (20% ointment) or MAL (16% ointment), after which the tumor was resected. After tumor resection, the mean number of additional MMS resection steps required to completely remove the tumor was 1.37±0.75. In 29 patients who underwent resection without FD (control group), the average number of additional resections was 1.83±0.89 ($p = 0.02$). In the FD group, 29 cases (76.3%) required one additional resection to completely remove the tumor, while nine (23.7%) required two or more resections. In the group without FD, one additional resection was required in 13 cases (44.8%) for complete excision of the tumor, while in 16 cases (55.2%) two or more resections were required ($p = 0.008$).

The literature describes attempts to use the FD method for the differential diagnosis of tumor and precancerous skin diseases with determining the stage of the disease by fluorescence intensity. So, T. Smits et al. [17] demonstrated that fluorescent diagnostics with 5-ALA derivatives cannot be used as a non-invasive diagnostic procedure to differentiate different stages of actinic keratosis, since no significant differences in fluorescence were found between different stages of actinic keratosis. However, fluorescent contrast is generally higher in Bowen's disease than in KIN I and KIN II lesions. The highest fluorescent contrast was found in

squamous cell carcinoma lesions, but the small number of such lesions (3 out of 86 biopsied lesions were classified as SCC) and the fact that they belonged to the same patient prevented a reliable statistical comparison. In further studies [18], the authors showed that only KIN I and KIN III foci show significant differences in fluorescent contrast values (1.3 and 2.5, respectively; $p<0.05$). The highest contrast ratios were determined in the foci of microinvasive SCC – 2.7.

A number of studies have shown the high efficacy of FD in patients with extramammary Paget's disease (EMPD). In the work of M. Wan et al. [19] in 21 patients with EMPD, the margin of the tumor lesion was determined by the FD method (photosensitizer – 20% 5-ALA ointment, exposure time 3.5 h) and the method of multiple exploratory biopsies (MSBs). The authors showed a strong correlation between the margin of the tumor lesion, determined by the FD method, and the margin, determined by the biopsy method with histological examination.

The high diagnostic value of FD in EMPD was also confirmed in the study by M. Wu et al. [20] The study included 36 patients. 5-ALA was used as a photosensitizer in the form of a 20% solution with an exposure time of 2 h. Tumor margin were determined visually, using FD and FD methods in combination with reflective confocal microscopy. 130 samples were taken from patients, in which the tumor process was confirmed. Out of 130 sections with a pathologically confirmed tumor process, 83 sections (63.8%) were located outside the macroscopically defined margin of tumor foci with a distance of 3.5±3.1 mm and a median of 2.7 mm; 46 (35.4%) sections were beyond the borders of the marker line of tumor foci, determined by the FD method with a distance of 2.1±1.7 mm and a median of 1.5 mm; 27 (20.8%) sections – outside the FD marker line with reflective confocal microscopy with a distance of 1.4±1.2 mm and a median of 0.9 mm.

Despite the high sensitivity and specificity of skin cancer FD, the development of modified FD methods aimed at increasing these parameters continues. For example, van der Beek et al. [21] presented the results of a study demonstrating a significant increase in the specificity and sensitivity of FD with 5-ALA in the form of a liposomal spray using the normalized fluorescence method. This approach reduces the contribution of external factors that distort the fluorescence intensity of PPIX, such as reflection due to non-perpendicular light hitting the skin, absorption of radiation by a thicker stratum corneum, or a change in radiation intensity due to a difference in the distance between the skin and the light source. The technique is based on the simultaneous measurement of PPIX-mediated fluorescence and autofluorescence after exposure to pulsed light with a wavelength of 407 nm. The source of autofluorescence is most likely bound collagen. Since the emission spectra of autofluorescence and fluorescence of PPIX are separated, it is technically possible to simultaneously measure autofluorescence in the green region of the spectrum and fluorescence and fluorescence of PPIX in the red region of the spectrum. At the same time, the system calculates the normalized fluorescence of PPIX. As a result, if there is a variable that affects the intensity of both types of fluorescence, it is possible to filter out this "noise" using data on the intensity of autofluorescence. The recorded fluorescence intensity is visualized with a pseudo color overlay, where red indicates the highest fluorescence and blue indicates the lowest fluorescence in the image. The analyzed focus was considered potentially suspicious for the presence of a pathological process when the fluorescence intensity (normalized or not) was exceeded by 33% or more than fluorescence in normal skin. The use of the normalized fluorescence assessment technique made it possible to increase the sensitivity of FD from 39% to 97% and the specificity from 27% to 100%.

FD can be used not only to determine the margin of a tumor lesion, but also as a method for monitoring the effectiveness of treatment. So, in the study by M. Bosseila et al. [22] evaluated the change in the fluorescent contrast of mycosis fungoides in 22 patients using fluorescence spectroscopy with 20% 5-ALA ointment (3-hour exposure). Diagnosis was performed twice, before and after specialized treatment for 12 weeks, including PUVA therapy with 8-methoxypsoralen and narrowband medium wave UVB therapy (311 nm) in combination with subcutaneous injection of IFN-αinterferon into resistant lesions. Studies have shown that the positive dynamics, confirmed by a decrease in the level of malignant CD4+/CD7– T cells, was accompanied by a decrease in the average fluorescent contrast from 2.2 to 1.94 ($p = 0.009$). Based on the data obtained, the authors conclude that in the case of mycosis fungoides, fluorescent diagnostics can be an effective tool for assessing the response of the tumor focus to therapy.

J. de Leeuw et al. [23] suggested using the FD method for screening for tumor and precancerous diseases in people working outdoors and exposed to constant UV radiation. The study involved 93 volunteers. In each patient, two drugs were used as a pro-photosensitizer: 5-ALA and MAL, which made it possible to compare their effectiveness. MAL in the form of a 16% cream was applied under an occlusive dressing on the right side of the forehead for 3 hours. Liposomal spray 5-ALA 0.5% was applied every 5 minutes on the left side of the forehead without occlusion for 2.5 hours, followed by 0 5-hour pause to allow the 5-ALA liposomes to fully absorb into the skin. Immediately afterward, fluorescent images were taken of both sides of the forehead. The fluorescent image of

the right (MAL treated) side of the forehead showed a very high and uniform fluorescence intensity in most of the examined skin areas with little difference between normal and diseased skin. The left side (treated with 5-ALA liposomal spray) in most cases showed low fluorescence of normal skin and moderate but distinct fluorescence of non-melanocytic skin tumor foci. At the same time, the authors note that the significantly lower absorption of 5-ALA in liposomes in normal skin leads to a lower degree of photosensitivity, and the faster clearance of 5-ALA provides a better safety profile compared to MAL cream (8 hours versus 36 hours of photosensitivity). As a result of the study, fluorescence was detected in 287 lesions in 61 patients. According to histological examination in 28 patients, positive fluorescence was detected in 212 benign lesions. Including 22 patients in 204 fluorescent foci, sebaceous hyperplasia was diagnosed, and the remaining 8 foci of false positive fluorescence in 6 patients corresponded to viral warts, benign lichenoid inflammation and dysplastic melanocytic nevi. In 29 patients, actinic ketosis was histologically confirmed in 71 fluorescence foci. 4 patients had 3 foci of BCC and 1 lesion of SCC. False-negative fluorescence was detected in only one lesion located on the scalp (negative fluorescent detection of a lesion clinically suspected and histologically confirmed as actinic keratosis). In 5 patients, 5 foci of actinic keratosis were detected by a fluorescent method and subsequently confirmed by histological examination, previously not noted by either the patients or the doctors who conducted the examination. When the fluorescence detection system used in this study was combined with clinical examination and dermatoscopy, the specificity of this method was 92%.

One paper was found in the literature devoted to evaluating the effectiveness of the use of photosensitizers for FD not based on 5-ALA and its derivatives. So, in the work of S.V. Kamrava et al. [24] FD with a photosensitizer based on chlorin e6 was performed in 40 patients with SCC (i.v. administration at a dose of 1.0 mg/kg 4-6 hours before diagnosis). The sensitivity of the method was 90%, specificity – 80%, accuracy – 87.5%, positive predictive value – 93%, negative predictive value – 72%.

In table the results of the main studies on the effectiveness of FD in nonmelanocytic skin tumors are summarized.

Таблица

Сводные данные результативности применения флуоресцентной диагностики у пациентов с немеланоцитарными опухолями кожи

Table

Summary data on the effectiveness of the use of fluorescence diagnostics in patients with non-melanoma skin cancer

	Авторы Authors	Число пациентов Number of patients	Диагноз Diagnosis	Фотосенсибилизатор Photosensitizer	Длина волны излучения Radiation wavelength	Результаты Results
1	Won и соавт. 2007, [9] Won et al. 2007, [9]	10 пациентов 10 patients	БКРК BCC	МЭ-АЛК 20% мазь MAL 20% ointment	Лампа Вуда, λ макс 365 нм Wood's lamp, λ max 365 nm	Чувствительность 82,6% Специфичность 94,1% Sensitivity 82.6% Specificity 94.1%
2	Smits и соавт. 2007, [17] Smits et al. 2007, [17]	14 пациентов 14 patients	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	Ксеноновая лампа с фильтром 370-440 нм Xenon light source with a custom band pass filter 370–440 nm	Не обнаружено существенных различий во флуоресценции между различными стадиями актинического кератоза. Флуоресцентная контрастность при болезни Боуэна, как правило, выше, чем при поражениях KIN I и KIN II No significant differences in fluorescence were found between different stages of actinic keratosis. Fluorescent contrast in Bowen's disease is generally higher than in KIN I and KIN II lesions

3	Neus и соавт. 2008, [7] Neus et al. 2008, [7]	28 пациентов 28 patients	БКРК BCC	5-АЛК 20% мазь 5-ALA 20% ointment	Лампа Вуда, λ макс 365 нм Wood's lamp, λ max 365 nm	Частота полного удаления опухолевого очага БКРК – 85,7%, неполного удаления – 14,3%. Чувствительность – 79% Специфичность – 100% The frequency of complete removal of the tumor focus of BCC is 85.7%, incomplete removal is 14.3%. Sensitivity – 79% Specificity – 100%
4	de Leeuw и соавт. [23] 2009 de Leeuw et al. [23] 2009	93 пациента 93 patients	Скрининг опухолевых и предопухолевых заболеваний у людей, работающих на улице и подвергающихся постоянному воздействию УФ-излучения Screening for neoplastic and preneoplastic diseases in people who work outdoors and are constantly exposed to UV radiation	5-АЛК (0,5% 5-АЛК, инкапсулированная в однослойные липосомы размером 50 нм; спрей 5-АЛК 0,5% каждые 5 мин в течение 2,5 ч на пораженный участок кожи) МЭ-АЛК 16% мазь (экспозиция 3 ч) 5-ALA 0.5% 5-ALA encapsulated in 50 nm sized unilamellar liposomes The 5-ALA 0.5% spray every 5 minutes for 2.5 hours to the involved skin area MAL 16% ointment (exposure 3 hours)	LED, λ макс 450 нм LED, λ max 450 nm	Положительная флуоресценция обнаружена у 61 пациента. Из них у 28 – доброкачественные поражения (в том числе у 22 – гиперплазия сальных желез), у 33 – опухолевая и предопухолевая патология (в том числе у 29 – актинический кератоз, у 3 – БКРК, у 1 – ПКРК) Positive fluorescence was found in 61 patients. Of these, 28 had benign lesions (including 22 had sebaceous gland hyperplasia), 33 had tumor and precancerous pathologies (actinic keratosis in 29, BCC in 3 and SCC in 1 patient)
5	Liutkeviciūte-Navickiene и соавт. 2009, [8] Liutkeviciūte-Navickiene et al. 2009, [8]	126 пациентов 126 patients	ПКРК и БКРК SCC and BCC	5-АЛК и МЭ-АЛК (экспозиция 2-4 ч) 5-ALA and ME-ALA (exposure 2-4 hours)	λ макс 378-426 нм λ max 378-426 nm	Чувствительность 95,4% Специфичность 88,6% Положительная прогностическая ценность 6,1% Отрицательная прогностическая ценность 96,3% В 30% случаев границы опухолевой ткани при применении МЭ-АЛК определялись более четко, чем при применении 5-АЛК Sensitivity 95.4% Specificity 88.6% Positive predictive value 6.1% Negative predictive value 96.3% In 30% of cases, the margin of the tumor tissue were more clearly defined with MAL than with 5-ALA
6	Kleinpenning и соавт. 2010, [18] Kleinpenning et al. 2010, [18]	13 пациентов 13 patients	36 очагов, в том числе 7 ПКРК, 17 актинический кератоз (5 KIN I, 6 KIN II, 6 KIN III), 3 БКРК, 9 нормальная кожа 36 lesions, including 7 SCC, 17 actinic keratosis (5 KIN I, 6 KIN II, 6 KIN III), 3 BCC, 9 normal skin	МЭ-АЛК 16% мазь MAL 16% ointment	Ксеноновая лампа с фильтром 370-440 нм Xenon light source with a custom band pass filter 370–440 nm	Только очаги KIN I и KIN III показывают достоверные различия в значениях флуоресцентной контрастности (1,3 и 2,5, соответственно; $p<0,05$). Самые высокие коэффициенты контрастности были определены у очагов микроинвазивного плоскоклеточного рака – 2,7 Only KIN I and KIN III foci show significant differences in fluorescent contrast values (1.3 and 2.5, respectively; $p<0.05$). The highest contrast ratios were determined in foci of microinvasive squamous cell carcinoma – 2.7

7	Kamrava и соавт. 2012, [24] Kamrava et al. 2012, [24]	40 пациентов 40 patients	ПКРК SCC	Хлорин е6 1 мг/кг за 4-6 ч до ФД Chlorine e6 1 mg/kg 4-6 hours before FD	λ макс 633 нм λ max 633 nm	Чувствительность 90% Специфичность 80% Точность 87,5% Положительная прогностическая ценность 93% Отрицательная прогностическая ценность 72% Sensitivity 90% Specificity 80% Accuracy 87.5% Positive predictive value 93% Negative predictive value 72%
8	Van der Beek и соавт. 2012, [21] Van der Beek et al. 2012, [21]	30 пациентов 30 patients	БКРК Актинический кератоз BCC, actinic keratosis	5-АЛК 5-ALA	λ макс 407 нм λ max 407 nm	Специфичность и чувствительность метода ненормированной флуоресценции существенно ниже, чем у метода обнаружения нормированной флуоресценции (27% и 39% против 100% и 97%) The specificity and sensitivity of the non-normalized fluorescence method is significantly lower than that of the normalized fluorescence detection method (27% and 39% versus 100% and 97%)
9	Jeon и соавт. 2013, [16] Jeon et al. 2013, [16]	38 пациентов в группе ФД и 29 пациентов в контрольной группе 38 patients in the FD group and 29 patients in the control group	ПКРК SCC	19 пациентов: МЭ-АЛК 16% мазь Экспозиция 3 ч 19 пациентов: 5-АЛК 20% мазь Экспозиция 6 ч 19 patients: MAL 16% ointment Exposure 3 hours 19 patients: 5-ALA 20% ointment Exposure 6 hours	Лампа Вуда, λ макс 356 нм Wood's lamp, λ max 365 nm	После резекции опухоли среднее количество дополнительных резекций по Моосу, понадобившихся для полного удаления опухоли, было ниже в группе ФД (1,37±0,75), чем в группе без ФД (1,83±0,89) After tumor resection, the mean number of additional Mohs resections required to completely remove the tumor was lower in the FD group (1.37±0.75) than in the non-FD group (1.83±0.89)
10	Andrade и соавт. 2014, [6] Andrade et al. 2014, [6]	43 пациента 43 patients	71 lesions, including 29 BCC, 31 actinic keratosis, 11 seborrheic keratosis	5-АЛК 5% раствор 5-АЛК был использован для 54 очагов (21 БКРК, 22 актинический кератоз, 11 себорейный кератоз). 10% раствор – для 17 очагов (8 БКРК и 9 актинический кератоз) 5-ALA 5% 5-ALA solution was applied on 54 lesions (21 BCCs, 22 AK, and 11 SK). 10% ALA solution was applied on 17 lesions (8 BCCs and 9 AK)	LED, λ макс 400 нм, 50 мВт/см^2 LED, λ max 400 nm, 50 mW/cm^2	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 foci of BCC, a significant increase in fluorescence intensity by 3 times was noted 1 hour after the application of the 5-ALA solution. In the foci of actinic and seborrheic keratosis, the fluorescence intensity remained at the autofluorescence level for 1 hour after application of the 5-ALA solution
11	Filonenko 2015, [2] Filonenko 2015, [2]	227 пациентов 227 patients	БКРК, ПКРК, метатипичный рак кожи BCC, SCC, metatypical skin cancer	5-АЛК (раствор для приема внутрь 1 мг/кг за 3 ч до ФД) 5-ALA (oral solution 1 mg/kg 3 hours before FD)	LED, λ макс 400-405 нм, LED, λ max 400-405 nm	Чувствительность 100,0% Специфичность 55,6% Sensitivity 100.0% Specificity 55.6%

12	El Hoshy и соавт. 2016, [15] El Hoshy et al. 2016, [15]	27 пациентов 27 patients	БКРК BCC	5-АЛК 20% мазь 5-ALA 20% ointment	Ксеноновая лампа с фильтром 370-440 нм Xenon light source with a custom band pass filter 370-440 nm	В 12 (44,44%) очагах границы опухоли, определенные по ФД, полностью совпали с границами, определенными гистопатологически. В 14 очагах гистопатологически границы опухоли были больше на 1 мм, чем определяемые по ФД, в 1 – больше на 2 мм In 12 (44.44%) foci, the margin of the tumor, determined by FD, completely coincided with the margin determined histopathologically. In 14 foci, histopathologically, the margin of the tumor were 1 mm larger than those determined by FD, and in 1 foci, they were 2 mm larger
13	Wan и соавт. 2018, [19] Wan et al. 2018, [19]	21 пациент 21 patients	ЭМРП EMPD	5-АЛК 20% мазь 5-ALA 20% ointment	Лампа Вуда, λ макс 365 нм Wood's lamp, λ max 365 nm	Показана сильная корреляцию между границами опухолевого поражения, определенными методом флуоресцентной диагностики, и границами, определенными методом биопсии с гистопатологией A strong correlation was shown between the margin of the tumor lesion, determined by the method of fluorescence diagnostics, and the margin, determined by the method of biopsy with histopathology
14	Wu и соавт. 2021, [20] Wu et al. 2021, [20]	36 пациентов 36 patients	ЭМРП EMPD	5-АЛК 20% раствор 5-ALA 20% solution	Лампа Вуда, λ макс 365 нм Wood's lamp, λ max 365 nm	Визуальный осмотр – 63,8% ложноотрицательных результатов, ФД – 35,4% ложноотрицательных результатов, ФД + конфокальная микроскопия – 20,8% ложноотрицательных результатов Visual examination – 63.8% of false negative results, FD – 35.4% of false negative results, FD + confocal microscopy – 20.8% of false negative results

*ФД – флуоресцентная диагностика, 5-АЛК – 5-аминолевулиновая кислота, МЭ-АЛК – метиловый эфир 5-аминолевулиновой кислоты, БКРК – базальноклеточный рак кожи, ПКРК – плоскоклеточный рак кожи, ЭМРП – экстрамаммарный рак Педжета
*FD – fluorescent diagnostics, 5-ALA – 5-aminolevulinic acid, MAL – 5-aminolevulinic acid methyl ester, BCC – basal cell carcinoma, SCC – squamous cell carcinoma, EMPD – extramammary Paget's desease

Conclusion

The main indications for FD with 5-ALA are the identification of clinically poorly expressed skin tumors, the search for hidden foci of precancer and skin cancer, as well as the clarification of the margin of the tumor lesion and monitoring the effectiveness of various specialized treatment options.

PPIX-induced fluorescence during preoperative planning is a valuable method for determining the peripheral margin of the tumor. The edges of tumors determined by histological mapping during tumor removal by Mohs micrographic surgery correlate well with the margin detected by tumor-specific fluorescence, which indicates the possibility of using fluorescence diagnostics as a full-fledged alternative to Mohs micrographic surgery – one of the most accurate, but rather labor-intensive and technically complex method determination of the margin of skin cancer foci.

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