REVIEWS OF LITERATURE

PHOTODYNAMIC THERAPY IN THE TREATMENT OF EXTRAMAMMARY PAGET'S DISEASE

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Abstract

Extramammary Paget's disease (EMPD) is a rare tumor that predominantly affects the skin containing apocrine glands. Due to insufficient data on the effectiveness of different methods, there is no single therapeutic approach to the treatment of patients with EMPD and their subsequent management. The use of surgical methods, laser therapy and local cytotoxic drugs has a number of limitations. The advantages of using photodynamic therapy (PDT) in EMPD are the absence of systemic toxicity, non-invasiveness, selectivity of action, the absence of carcinogenic potential, the possibility of conducting several courses of treatment, and good cosmetic results. In our review, we analyzed those published in 2000-2022 data on the results of PDT treatment of 114 patients with EMPD. As a result of treatment, complete regression of tumor foci was achieved in 40% of patients. Most authors note that PDT is more effective for small areas (up to 4 cm^2).

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

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ЛЕЧЕНИИ ЭКСТРАМАММАРНОГО РАКА ПЕДЖЕТА

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Резюме

Экстрамаммарный рак Педжета (ЭМРП) – редко встречающаяся опухоль, которая преимущественно поражает кожу, содержащую апокринные железы. Из-за недостаточного количества данных по эффективности разных методов отсутствует единый терапевтический подход к лечению пациентов с ЭМРП и их последующего ведения. Применение хирургических методов, лазерной терапии и местных цитостатических препаратов имеет ряд ограничений. Преимуществами использования при ЭМРП фотодинамической терапии (ФДТ) являются отсутствие системной токсичности, неинвазивность, избирательность действия, отсутствие канцерогенного потенциала, возможность проведения нескольких курсов лечения и хорошие косметические результаты. В нашем обзоре проанализированы опубликованные в 2000-2022 гг. данные о результатах лечения методом ФДТ 114 пациентов с ЭМРП. В результате лечения полная регрессия опухолевых очагов была достигнута у 40% пациентов. Большинство авторов отмечают, что ФДТ эффективнее при очагах небольшой площади (до 4 $см^2$).

Ключевые слова: фотодинамическая терапия, экстрамаммарный рак Педжета, 5-аминолевулиновая кислота, фотофрин, метиловый эфир 5-аминолевулиновой кислоты.

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Epidemiology

Extramammary Paget's disease (EMPD) is a rare, slow–growing intraepithelial adenocarcinoma that predominantly affects the skin containing apocrine glands, such as the perianal, genital, and axillary areas of the body. Elderly people are more often diagnosed with EMPD than the others, with such disease characteristics as slow development and progression [1-3]. Women tend to be exposed to EMPD more than men (3-4,5:1) [4]. In the case of ineffective treatment, the disease progresses into invasive and metastatic forms.

The frequency and prevalence of EMPD are not precisely determined, although the disease is generally considered to be rare. Most of the notes on EMPD in the dermatological literature over the past decades were reports about individual clinical observations. Due to the rare occurrence of EMPD, conducting full-fledged prospective multicenter clinical trials is difficult. Hence, there are no reports of such studies in the literature [5]. On average, the incidence of EMPD is estimated as only 0.12 per 100,000 people and constitute 21% of primary cases of scrotal cancer, 1-2% of primary cases of vulvar cancer [2, 6]. At the same time, Paget's mammary cancer accounts for 0.7-4.3% of all cases of breast cancer [7]. EMPD accounts for only 6.5% of all forms of Paget's disease [8]. In Germany, the number of new cases of EMPD is estimated at the level of 20-126 cases per year [5], in the Netherlands – 17 cases per year [9].

Clinic

EMPD affects areas of the skin containing apocrine sweat glands. Predisposition areas include the anogenital region and, less often, the armpits. A study conducted by J.J. Chanda et al. with the participation of 197 patients with EMPD showed that 128 (65%) patients had vulva affected, 29 (15%) patients had tumor in perianal areas, and another 27 (14%) patients had penis, scrotum or inguinal area affected [10]. In cases involving the vulva, in most cases, a tumor occurs on the labia majora [9].

Clinically, EMPD lesions are often manifested by infiltrative erythema with crusts and scales, sometimes resembling other skin diseases, such as eczema [1].

There are primary and secondary forms of EMPD. While primary EMPD occurs as an intraepithelial neoplasm of the epidermis, secondary EMPD develops as a result of the epidermotropic or direct spread of malignant cells from the main primary focus of the malignant neoplasm such as, usually, the lower gastrointestinal tract or urinary tract. As the treatment strategy and prognosis for primary and secondary EMPD differ, an accurate diagnosis based on a detailed histopathological assessment of a variety of immunohistochemical markers is required. In most cases, EMPD is diagnosed as carcinoma in situ, which usually demonstrates a slow progression of the disease. However, once Paget cells penetrate deep into the dermis, the risk of developing metastases in regional lymph nodes increases [1, 3].

Despite its slow progression, EMPD does not respond well to therapy. The overall 10-year survival rate for EMPD is about 60% after diagnosis [11].

The clinical manifestations of EMPD can vary significantly depending on the area and localization of the affected area and the duration of the disease. The primary lesion is usually represented by a red spot with sharp borders. Spots with depigmentation or hyperpigmentation may appear. The color can vary from pink, light red or dark red to red brown. In particular, larger lesions may have a mixed color. Larger, more common lesions may be irregularly shaped with poorly defined borders. The centrifugal nature of growth leads to the formation of uneven boundaries, the appearance of which is considered to be a characteristic feature of EMPD. The surface of the lesion may have a rough lamellar plaque depending on the affected area [5].

Diagnostics

Due to the similarity of the clinical picture with many benign conditions, the diagnosis of EMPD is often postponed for years, and only every fifth patient is correctly diagnosed at the first appointment [12]. More often, EMPD manifests itself in the form of well-defined or poorly defined erythematous and scaly plaques, which can become crusted, ulcerate, or acquire pigmentation [2]. But at an early stage, the most common symptoms are itching, rash or erythema, which usually do not cause any special suspicion of malignant etiology. Initial differential diagnoses are contact dermatitis, seborrheic eczema, and fungal infections. Patients with EMPD are often treated for the mentioned above diseases for several years with the use of the conservative treatment such as local emollients or corticosteroids, antifungal creams or other oral treatments. And only after a long period of unsuccessful treatment, an additional diagnosis is carried out. As a result, the correct diagnosis is postponed for several years [2].

The biopsy of the lesion helps to establish the final diagnosis. Characteristic signs of EMPD are a thickened epidermis with papillomatosis, an increase in interpapillary furrows, hyperkeratosis or parakeratosis on the surface, and characteristic Paget cells with transparent abundant cytoplasm. The cytoplasm of these cells is positive for Schiff acid staining and

resistant to diastasis, which indicates the presence of neutral polysaccharides and confirms the glandular origin of the cells. Markers of the glandular epithelium are also a positive reaction to staining with antibodies to carcinoembryonic antigen (CEA), low molecular weight cytokeratin (Cam 5.2), and cytokeratin 7 (CK7). Histological examination of the EMPD focus usually reveals epidermal infiltration of Paget cells, which look like large round cells with abundant pale pink cytoplasm surrounding hypochromatic nuclei, sometimes with a protruding nucleolus [13, 14].

Treatment

Due to the rare occurrence of EMPD, there are disagreements regarding therapeutic approaches to the treatment of patients with EMPD and their subsequent management. Currently, the recommendations for the EMPD treatment are based only on the published results of several series of clinical observations of individual institutions and small reports on individual clinical observations, with many different therapy options. Hence, it is difficult to compare and evaluate their effectiveness [2].

Several invasive and non-invasive EMPD treatment options are used with limited comparative data for the EMPD treatment.

Surgical treatment

Although there are no established guidelines for the EMPD treatment, surgical resection is the generally accepted standard of practice. In particular, wide local excision with edges from 1 to 5 cm is widely used, but its use may be associated with a high frequency of relapses. In several studies, it has been demonstrated that Mohs micrographic surgery provides high efficiency of treatment with a lower probability of relapses [2, 3, 15]. In case of Mohs micrographic surgery use, 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. Mohs micrographic surgery provides an intraoperative microscopic assessment of 100% of the lesion edges, which makes it possible to remove only the affected tissue and reduce the recurrence rate [16].

The problem with the use of Mohs micrographic surgery, as well as any other option for surgical treatment of EMPD, is that most cases of EMPD are represented by extensive lesions of a significant area. In addition, the disease primarily affects the elderly people. Not all of whom can undergo surgery. The necessary procedures in the surgical treatment of anogenital diseases (for example, vulvectomy, installation of a skin-muscle flap or artificial anus) often lead to a significant decrease in the quality of life [5]. In addition, many researchers note a rather high risk of recurrence after surgical treatment of EMPD. Thus, according to J.D. Zollo et al. [17], the average recurrence rate after surgical treatment for all EMPD localities is 35-44%. Hence, there is considerable interest in less invasive therapeutic approaches due to the potential slow progression of the disease and limitations in the use of surgical methods of treatment [15].

Local therapy

One of the alternatives to surgical intervention is the use of local cytostatic and other medications. In the studies of H.F. Haberman et al. [18] and Kawatsu T. and co-author. [19], it was shown that the use of 5-fluorouracil in the treatment of the genital form of EMPD makes it possible to eliminate the clinical manifestations of the disease. At the same time, the results of the biopsy showed the preservation of pathological cells, which indicates a low effectiveness of treatment. W.G. Watring et al. [20] reported a complete therapeutic response to topical bleomycin treatment in the case of 4 out of 7 patients with recurrent vulvar EMPD. One of the 4 patients had a relapse of the disease after 30 months, which required repeated treatment.

Another medicine for local therapy in EMPD treatment is imiquimod (an immunomodulator and modifier of the immune response, which enhances both innate and acquired immunity by stimulating the production of cytokines such as interferon-α and tumor necrosis factor-α). These cytokines, in turn, activate the antitumor immune system, increasing the death and destruction of tumor cells [2]. According to H. Machida et al. [21], the therapeutic efficacy of imiquimod in the treatment of EMPD reaches 52-80% with a recurrence rate of 19%.

Laser therapy

The advantages of using CO_2 and Nd:YAG lasers for the treatment of EMPD include non-invasiveness and a reduction in the duration of hospitalization compared to surgical intervention. However, the lack of histological data for analysis, postoperative pain and anesthesia requirements reduce the therapeutic value of this treatment method [2]. Some researchers note a high recurrence rate (up to 67-100%) in the case of using this method in the treatment of multifocal, extensive, and invasive lesions of EMPD [22, 23].

Photodynamic therapy

Photodynamic therapy (PDT) is a minimally invasive method of antitumor therapy, it is a procedure involving local or systemic administration of a photosensitizer that is selectively localized in tumor tissues. Subsequent activation of the medicine by a light source leads to the formation of reactive oxygen species, which causes the death of tumor cells. The advantages of PDT include low toxicity, the possibility of repeated courses without the development of resistance to treatment, preservation of organ function and good cosmetic results, as well as the possibility of use combined with other methods of treatment [3, 24-26]. The experience of using PDT in the treatment of EMPD estimates more than 30 years. However, most of the data in the literature on this topic are reports of single clinical observations with PDT in various modes, often using different photosensitizers treating one patient. In the available literature, there are no systematic reviews, meta-analyses of the effectiveness of the use of different PDT regimens in the treatment of EMPD or reports on the results of full-scale prospective clinical studies of the effectiveness of PDT in EMPD. These reasons significantly complicate the development of a single tactic for effective treatment of EMPD by PDT.

This review systematizes the results of EMPD treatment by PDT in mono-mode according to publications on pubmed.com for 2000-2022. We analyzed the results of PDT in the treatement of 114 patients with EMPD. The number of foci was indicated only in some publications, so it is not possible to estimate their total number. For PDT, ointments with 5-aminolevulenic acid (5-ALA) (29 patients) and 5-ALA methyl ether (67 patients) were most often used, photophrine (4 patients) and a hematoporphyrin derivative (11 patients) were also used. In the case of 3 patients, treatment was carried out using 5-ALA and photophrine (for different foci or sequentially for one focus).

There are no comparative data on the effectiveness of different photosensitizers for PDT in EMPD. Some authors point to a higher efficiency of PDT using photophrine compared to the local application of ointment based on 5-ALA. Thus, V. Madan et al. [27] reported the results of treatment of an 80-year-old patient with an extensive invasive focus of scrotal EMPD with an area of 100 cm^2, secondary to prostate adenocarcinoma by PDT. The patient had a relapse of the disease in 9 months after 5 courses of PDT with local application of 20% 5-ALK ointment. The patient underwent PDT with photofrin. Within 1 year after treatment, the patient was observed without registered relapse. Based on the obtained results, the authors of the study point to the high efficiency of PDT using photophrine. In the study of S. Shieh et al. [28] after PDT of 16 EMPD foci with 20% 5-ALA ointment, complete regression was obtained in 50% of cases (8 foci). One focus with partial regression of the tumor was additionally treated with PDT with photofrin at a dose of 1 mg/kg; the result was assessed as a complete regression with an effect duration of 71 months. Despite these isolated reports of the high efficacy of photophrine, a small amount of data does not allow us to draw reasonable conclusions about the benefits of its use for the treatment of EMPD.

Many patients treated with PDT had of a large area of EMPD foci. Thus, the lesion area in one of the patients exceeded 75 cm^2 in the study of X.L. Wang et al. [29], and the lesion area was about 100 cm^2 in the case of the patient described in the study V. Madan et al. [27]. Many authors note that the direct effect of PDT depends on the area of the treated focus. Thus, both patients in these studies had only partial regression of the tumor after PDT. In the work of R. Fontanelli et al. [30], it was noted that, during the treatment of patients with small formations (with a size of up to 5 cm^2), complete regression was obtained in the case of 50% of patients, with a size of 5-10 cm^2 foci – in 10% of cases, more than 10 cm^2 – in 0%.

The long-term effects of PDT also depend on the area of the EMPD focus. Q. Li et al. [31] note the relationship between the frequency of relapses and the area of the focus treated by PDT. In this study, both relapses registered within 12 months after PDT occurred in the case of the patients who had a focus area of more than 4 cm^2 (in total, 13 patients with a focus area of more than 4 cm^2 participated in the study). None of the patients with a focal area of less than 4 cm^2 (8 patients) had relapses for these periods. In the study of M. Magnano et al. [32], complete tumor regression was achieved after PDT treatment of a patient with a 15 cm^2 EMPD lesion. However, after 2 months, the patient had a relapse of the disease.

The main complication of PDT in patients with EMPD was severe pain during PDT. Q. Li et al. [31] report that 12 of the 16 patients who participated in the study could not withstand the acute pain caused by LED irradiation, and they were given anesthesia. The average intensity of pain on a scale from 1 to 10 was 5.4, including in case of perianal localization of the EMPD focus – 9.1, vulvar – 6.5, axillary 4.5 and scrotal – 3.2. At the same time, the study of F. Raspagliesi et al. [33] shows that pain was noted only in 1 out of 7 patients with vulvar localization of EMPD foci.

The table presents summary data on 15 publications dating from 2000 to 2022 (indexed in Pubmed) with the results of a study on the PDT effectiveness in a treatment of 114 patients with EMPD in total.

Таблица
Сводные данные результативности применения фотодинамической терапии у пациентов с ЭМРП
Table
Summary of the effectiveness of photodynamic therapy in patients with extramammary Paget's disease

Авторы Authors	Число пациентов/ количество очагов No. of lesions/ No. of patients	Локализация Localisation	Фотосенсибилизатор, доза Photosensitizer, dose	Световая доза, Дж/см² Light dose, J/cm²	Количество курсов ФДТ Number of PDT courses	Результат терапии Results of therapy	Рецидив Relapse	Срок наблюдения, мес Follow-up period, month
Runfola и соавт., 2000 [34] Runfola et al., 2000 [34]	1/7	Перианальная область Perianal area	Фотофрин 1 мг/кг Photofrin 1 mg/kg	210 Дж/см² 210 J/cm²	1 курс 1 course	Пациенты: ПР 100% (1/1) Patients: CR 100% (1/1)	Нет No	Не указано Not specified
Shieh и соавт., 2002 [28] Shieh et al., 2002 [28]	5/17	Пах, мошонка, половой, член, лобок Groin, scrotum, penis, pubis	5-АЛК 20% мазь, экспозиция 18-24 ч (17 очагов) Фотофрин 1 мг/кг (1 очаг) 5-ALA 20% ointment, exposure 18-24 hours (17 foci) Photofrin 1 mg/kg (1 focus)	100-400 Дж/см² 100-400 J/cm²	1-5 курсов (интервал 2 нед) 1-5 courses (interval of 2 weeks)	Очаги: ПР 53% (9/17) ЧР 18% (3/17) СТ % (29/17) Lesions: CR 53% (9/17) PR 18% (3/17) NC % (29/17)	После ФДТ с 5-АЛК и фотофрином – через 6 мес ПЭ, без рецидива 71 мес. После 5-АЛК – 3 рецидива через 9-10 мес, 13 без рецидива 6-29 мес. After PDT with 5-ALA and photofrin – after 6 months of PE, without relapse 71 months. After 5-ALA – 3 relapse after 9-10 months, 13 without relapse 6-29 months.	6-71 мес 6-71 months
Madan и соавт., 2005 [27] Madan et al., 2005 [27]	1/1	Мошонка Scrotum	5-АЛК 20% мазь, экспозиция 6 ч Фотофрин 1 мг/кг 5-ALA 20% ointment, exposure 6 hours Photofrin 1 mg/kg	100 Дж/см² 100 J/cm²	5 курсов ФДТ с 5-АЛК (интервал 1-9 мес), затем 1 курс ФДТ с фотофрином 5 courses of PDT with 5-ALA (interval of 1-9 months), then 1 course of PDT with photofrin	Пациенты: ПР 100% (1/1) Patients: CR 100% (1/1)	Рецидив через 9 мес после 5 курсов ФДТ с 5-АЛК. После ФДТ с фотофрином без рецидива 12 мес Relapse 9 months after 5 courses of PDT with 5-ALA. After PDT with photofrin without relapse 12 months	12 мес 12 months

Raspagliesi и соавт., 2006 [33] Raspagliesi et al., 2006 [33]	7/11	Вульва * у 2 пациентов также были поражения вне вульвы, у 3 – поражения большой площади (площадь не указана) Vulva * 2 patients also had lesions outside the vulva, 3 had lesions of a large area (area not specified)	Метиловый эфир 5-АЛК 20% мазь, экспозиция 3 ч 5-ALA methyl ester 20% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	2-3 курса (интервал 3 нед) 2-3 courses (interval of 3 weeks)	Очаги: ПР 73% (8/11) ЧР 9% (1/11) СТ 18% (2/11) * 2 ПР не подтверждены гистологически Lesions: CR 73% (8/11) PR 9% (1/11) NC 18% (2/11)	Нет No	1-5 мес 1-5 months
Wang и со-авт., 2008 [29] Wang et al., 2008 [29]	3/4	Половой член Penis	5-АЛК 10-20% раствор, экспозиция 3-5 ч 5-ALA 10-20% solution, exposure 3-5 h	80-100 Дж/см^2 80-100 J/cm^2	2 курса (интервал 2 нед) 2 courses (interval of 2 weeks)	Пациенты: ЧР 100% (3/3) Patients: PR 100% (3/3)	2 рецидива в течение 12 мес 2 relapses within 12 months	12 мес 12 months
Tanaka и соавт., 2009 [13] Tanaka et al., 2009 [13]	4/не указано 4/not stated	Вульва, мошонка, подмышечная впадина Vulva, scrotum, armpit	Метиловый эфир 5-АЛК 16% мазь, экспозиция 3 ч 5-ALA methyl ester 16% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	3-8 курсов (интервал не указан) 3-8 courses (interval is not mentioned)	Пациенты: ПР 25% (1/4) ЧР 75% (3/4) Patients: CR 25% (1/4) PR 75% (3/4)		6-12 мес 6-12 months
Li и соавт., 2010 [31] Li et al., 2010 [31]	17/21	Мошонка, подмышечная область, перианальная область, вульва Scrotum, axillary region, perianal region, vulva	5-АЛК 20% мазь, экспозиция 6 ч 5-ALA 20% ointment, exposure 6 hours	113 Дж/см^2 113 J/cm^2	3 курса (интервал 1 нед) 3 courses (1 week interval)	Очаги: ПР 52,4% (11/21) Lesions: CR 52,4% (11/21)	2 рецидива через 6-12 мес 2 relapses after 6-12 months	24 мес 24 months
Housel и соавт., 2010 [35] Housel et al., 2010 [35]	8/25	Мошонка, подмышечная область, перианальная область, лобок, ягодица, половой член Scrotum, axillary region, perianal region, pubis, buttock, penis	5-АЛК 20% мазь (16 очагов) Фотофрин 1-2 мг/кг (9 очагов) 3 пациента: фотофрин, 4 пациента: 5-АЛК, 1 пациент – 5-АЛК + фотофрин 5-ALA 20% ointment (16 foci) Photofrin 1-2 mg/kg (9 foci) 3 Patienst: Photofrin, 4 patients: 5-ALA, 1 patient-5-ALA + fotofrin	5-АЛК: 100-250 Дж/см^2 Фото-фрин: 215 Дж/см^2 5-ALA: 100-250 J/cm^2 Photo-frin: 215 J/cm^2	5-АЛК: 1-5 курсов Фотофрин: 1 курс 5-ALA: 1-5 courses Photofrin: 1 course	Очаги, пролеченные 5-АЛК: ПР 50% (8/16) ЧР 19% (3/16) СТ 31% (5/16) Очаги, пролеченные фотофрином: ПР 78% (7/9) ЧР 22% (2/9) Foci treated with 5-ALA: PR 50% (8/16) CR 19% (3/16) NC 31% (5/16) Foci treated with photo-frin: PR 78% (7/9) CR 22% (2/9)	3 рецидива через 9-10 мес 3 relapses after 9-10 months	3-96 мес 3-96 months

Kitagawa и соавт., 2011 [36] Kitagawa et al., 2011 [36]	1/1	Надлобковая зона Suprapubic zone	Метиловый эфир 5-АЛК 16% мазь, экспозиция 3 ч 5-ALA methyl ester 16% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	2 курса (интервал 1 нед) 2 courses (1 week interval)	Пациенты: ПР 100% (1/1) Patients: CR 100% (1/1)	Нет No	2 мес 2 months
Yousef и соавт., 2012 [37] Yousef et al., 2012 [37]	2/не указано 2/not stated	Вульва, лобок, мошонка Vulva, pubis, scrotum	Метиловый эфир 5-АЛК 16% мазь, экспозиция 3 ч 5-ALA methyl ester 16% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	3 и 9 курсов (интервал 2-4 нед) 3 and 9 courses (interval of 2-4 weeks)	Пациенты: ЧР 50% (1/2) СТ 50% (1/2) Patients: PR 50% (1/2) NC 50% (1/2)	Нет No	12 мес 12 months
Fontanelli и соавт., 2013 [30] Fontanelli et al., 2013 [30]	32/не указано 32/not stated	Вульва, перианальная область Vulva, perianal area	Метиловый эфир 5-АЛК 16% мазь, экспозиция 3 ч 5-ALA methyl ester 16% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	3 курса (интервал 3 нед) 3 courses (interval of 3 weeks)	После 3 курсов: Пациенты: ПР 9% (3/32) ЧР 78% (25/32) СТ 13% (4/32) After 3 courses: Patients: CR 9% (3/32) PR 78% (25/32) NC 13% (4/32)	Рецидивы у 3/3 пациентов с ПР через 6, 8 и 18 мес Relapses in 3/3 of patients with CR after 6, 8 and 18 months	6-18 мес после ПР 6-18 months after CR
Magnano и соавт., 2013 [32] Magnano et al., 2013 [32]	1/1	Вульва Vulva	Метиловый эфир 5-АЛК 16% мазь, экспозиция 3 ч 5-ALA methyl ester 16% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	3 курса (интервал 3 нед) После рецидива 3 курса (интервал 3 нед) 3 courses (interval of 3 weeks) After relapse of the 3rd course (interval of 3 weeks)	После 6 курсов ФДТ: Пациенты: ПР 100% (1/1) After 6 courses: Patients: CR 100% (1/1)	Рецидив через 2 мес после 3 курсов Relapse in 2 months after 3 courses	Не указано Not specified
Calzavara-Pinton и соавт., 2013 [38] Calzavara-Pinton et al., 2013 [38]	8/не указано 8/not stated		Метиловый эфир 5-АЛК 16% мазь, экспозиция 3-4 ч 5-ALA methyl ester 16% ointment, exposure 3-4 hours	37 Дж/см^2 37 J/cm^2	В среднем 2,4 курса (интервал 3 нед) On average, 2.4 courses (interval of 3 weeks)	Пациенты: ПР 13% (3/8) ЧР 50% (4/8) СТ 37% (1/8) Patients: CR 13% (3/8) PR 50% (4/8) NC 37% (1/8)	Не указано Not specified	8,5 мес 8,5 months

Rioli и соавт., 2018 [6] Rioli et al., 2018 [6]	13/не указано 13/not stated	Вульва Vulva	Метиловый эфир 5-АЛК 16% мазь, экспозиция 3 ч 5-ALA methyl ester 16% ointment, exposure 3 hours	37 Дж/см^2 37 J/cm^2	1-3 курса (интервал не указан) 1-3 courses (interval is not mentioned)	После 1 курса ФДТ: Пациенты: ПР 38% (2/13) ЧР 38% (5/13) СТ 16% (5/13) РО 8% (1/13) После 2 курса ФДТ: Пациенты: ПР 17% (1/6) СТ 66% (4/6) РО 17% (1/6) После 3 курса ФДТ: Пациенты: СТ 100% (2/2) After the 1st course of PDT: Patients: CR 38% (2/13) PR 38% (5/13) NC 16% (5/13) RO 8% (1/13) After the 2nd course of PDT: Patients: CR 17% (1/6) NC 66% (4/6) RO 17% (1/6) After the 3rd course of PDT: Patients: NC 100% (2/2)	7 рецидивов у 7/7 пациентов с ПР и ЧР после 1 курса ФДТ 7 relapses in 7/7 patients with CR and PR after 1 course of PDT	4-75 мес 4-75 months
Wang и соавт., 2022 [39] Wang et al., 2022 [39]	11/не указано 11/not stated	Вульва, половой член, мошонка, перианальная область Vulva, penis, scrotum, perianal area	Производное гематопорфирина 3-5 мг/кг Hematoporphyrin derivative 3-5 mg/kg	150-200 Дж/см^2 150-200 J/cm^2		Пациенты: ПР 91% (10/11) ЧР 9% (1/11) Patients: CR 91% (10/11) PR 9% (1/11)	2 рецидива у 2/10 пациентов с ПР через 12 мес 2 relapses in the case of 2/10 patients with CR after 12 months	12-27 мес 12-27 months

Примечания: ПР – полная регрессия, ЧР – частичная регрессия, СТ – стабилизация, РО – рост опухоли.
Note: CR – complete regression, PR – partial regression, NC – no change, TG – tumor growth.

Conclusion

As EMPD is a relatively rare disease, there are no clear treatment recommendations in the literature based on large, multicenter studies comparing the efficacy of different therapies. PDT shows good results of the tumor treatment, both immediate (up to 40% of patients had complete regression of EMPD foci) and long-term (relapses in the case of 21% of patients at follow-up periods of 2-29 months; relapses in most cases occurred during the treatment of a large area foci). The advantages of PDT are the absence of systemic toxicity, non-invasiveness, selectivity of action, the absence of carcinogenic potential, the possibility of conducting several courses of treatment, and good cosmetic results. The highest efficiency of PDT was noted for small foci treatment (up to 4 cm^2).

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