LASER TECHNOLOGIES IN TREATMENT OF CERVICAL INTRAEPYTELIAL NEOPLASIA (REVIEW)

Tzerkovsky D.A.[1], **Dunaevskaya V.V.**[2]
[1]N.N. Alexandrov National Cancer Centre of Belarus, Lesnoy, Republic of Belarus
[2]National Cancer Institute, Kiev, Ukraine

Abstract

This review article discusses the key aspects of the use of laser technologies, namely, laser vaporization (LV) and photodynamic therapy (PDT), in the treatment of patients with cervical intraepithelial neoplasia (CIN). The authors analyzed and systematized the foreign experience of these methods of treatment, their indications and contraindications, as well as the advantages over traditional approaches to the treatment of this pathology. The main advantages of the LV are the possibility of complete evaporation of the pathological focus, visual control over the depth of tissue destruction, the absence of prolonged edema and cicatricial deformities, which allows maintaining the integrity of the cervix and its reproductive function. Despite the low trauma and low frequency of adverse reactions, the data on the effectiveness of LV are quite contradictory and, according to various authors, vary from 50% to 98%. To date, there is a significant amount of accumulated experience in the use of PDT with various photosensitizing agents (5-aminolevulinic acid (5-ALA), hematoporphyrin and chlorin and their derivatives) in the treatment of patients with CIN. The main advantages of the PDT are minimal toxicity to the surrounding normal tissues due to the selective accumulation of photosensitizer in pathological tissues, a low risk of severe pain syndrome, the absence of mechanisms of primary and acquired resistance, the possibility of an outpatient treatment session, the possibility of combining with other methods of therapeutic action, the absence of limiting cumulative doses of photosensitizers and light exposure, the possibility of multiple repetitions of the session, good cosmetic results and the possibility of implementing an organ-preserving method of treatment. The obtained results indicate good tolerability of the method (no severe adverse reactions) and a fairly high efficiency of PDT: the frequency of complete regressions varies from 30% to 67% - for application forms of 5-ALA and from 90% to 98.1% - for hematoporifirin and chlorin photosensitizers. Thus, LV and PDT can be considered safe and effective treatment options for patients with CIN.

Key words: cervical intraepithelial neoplasia, laser vaporization, photodynamic therapy.

For citations: Tzerkovsky D.A., Dunaevskaya V.V. Laser technologies in treatment of cervical intraepithelial neoplasia (review), Biomedical Photonics, 2020, vol. 9, no. 3, pp. 30–39 (In Russian). doi: 10.24931/2413–9432–2020–9–3–30–39

Contacts: Tzerkovsky D.A., email: tzerkovsky@mail.ru

ЛАЗЕРНЫЕ ТЕХНОЛОГИИ В ЛЕЧЕНИИ ЦЕРВИКАЛЬНОЙ ИНТРАЭПИТЕЛИАЛЬНОЙ НЕОПЛАЗИИ (ОБЗОР ЛИТЕРАТУРЫ)

Д.А. Церковский[1], **В.В. Дунаевская**[2]
[1]Республиканский научно-практический центр онкологии и медицинской радиологии им. Н.Н. Александрова, Лесной, Республика Беларусь
[2]Национальный институт рака, Киев, Украина

Резюме

В представленной обзорной статье рассмотрены ключевые аспекты применения лазерных технологий, а именно лазерной вапоризации (ЛВ) и фотодинамической терапии (ФДТ), в лечении пациенток с цервикальными интраэпителиальными неоплазиями (CIN). Авторы проанализировали и систематизировали зарубежный опыт данных методов лечения, показания и противопоказания к их применению и преимущества по сравнению с традиционными подходами к лечению этой патологии. Основными преимуществами метода ЛВ являются возможность полного испарения патологического очага, визуальный контроль за глубиной деструкции тканей, отсутствие длительного отека и рубцовых деформаций, что позволяет сохранить целостность шейки матки и ее репродуктивную функцию. Несмотря на малую травматичность и невысокую частоту нежелательных реакций, данные литературы об эффективности ЛВ достаточно противоречивы и варьирует от 50% до 98%. В настоящее время в мире накоплен значительный опыт применения ФДТ с различными фотосенсибилизирующими агентами (5-аминолевулиновая кислота (5-АЛК), гематопорфирин, хлорин и их производные) в лечении пациенток с CIN. Основными преимуществами метода ФДТ являются минимальная токсичность для окружающих нормальных тканей в связи с избирательным накоплением фотосенсибилизатора (ФС) в патологических тканях, невысокий риск воз-

никновения выраженного болевого синдрома, отсутствие механизмов первичной и приобретенной резистентности, возможность амбулаторного проведения сеанса лечения, возможность комбинации с другими методами лечебного воздействия, отсутствие лимитирующих кумулятивных доз ФС и светового воздействия, возможность многократного повторения сеанса, хорошие косметические результаты и возможность реализации органосохраняющего метода лечения. Полученные результаты свидетельствуют о хорошей переносимости лечения и достаточно высокой эффективности применения ФДТ: частота полных регрессий варьирует от 30 до 67% при использовании аппликационных форм 5-АЛК, от 90 до 98,1% – при использовании гематопорифирина и хлориновых ФС. Таким образом, ЛВ и ФДТ могут рассматриваться как безопасные и эффективные опции лечения пациенток с CIN.

Ключевые слова: цервикальная интраэпителиальная неоплазия, лазерная вапоризация, фотодинамическая терапия.

Для цитирования: Церковский Д.А., Дунаевская В.В. Лазерные технологии в лечении цервикальной интраэпителиальной неоплазии (обзор литературы) // Biomedical Photonics. – 2020. – Т. 9, № 3. – С. 30–39. doi: 10.24931/2413–9432–2020–9–3–30–39.

Контакты: Церковский Д.А., email: tzerkovsky@mail.ru

Introduction

Cervical dysplasia or cervical intraepithelial neoplasia (CIN) is a serious disease caused by the presence of human papilloma viruses (HPV) of high oncogenic risk [1]. CIN is most commonly found in young women (25–35 y. o.). This is due to the fact that at this age, HPV elimination processes are already completed, and if they have not occurred, then the negative effect of the viruses can be activated.

There are three degrees of cervical dysplasia: light (CIN I), medium (CIN II) and severe (CIN III). All of them are links in the same chain, and it is believed that CIN I and CIN II are reversible processes, and CIN III is considered to be a precancerous disease. Due to the etiological role of HPV in cervical carcinogenesis, the initial stages of cervical cancer are regarded as HPV-associated diseases: HPV DNA is detected in 25% of cases of CIN I, in 80% of cases of CIN II, and up to 96% of cases of CIN III. The risk of malignancy is associated with the presence of several high-risk HPV genotypes: 16, 18, 31, 33, 35 and 45. It was found that the presence of oncogenic HPV genotypes serves as a prognostic factor for the development of CIN. HPV, mainly its 16 and 18 genotypes, is detected in 50–80% of spesimens of moderate and severe cervical squamous epithelium dysplasia and in 90% of cases of invasive cancer [2].

Timely diagnosis and effective treatment of CIN provide secondary prevention of cervical cancer [3]. The existing treatment methods can be divided into surgical and destructive ones. The first category includes cold-knife, laser and radio wave excision, and the second consists of laser vaporization (LV), diathermocoagulation and cryodestruction. All the listed methods of treatment have a direct impact on the pathological focus without affecting the mechanisms of disease development. However, their use may lead to the development of a number of undesirable reactions, such as pain, bleeding, lymphorrhea and tissue trauma, leading to the formation of rough scars on the cervix and the stenosis of the cervical canal, accompanied by changes in the anatomical structure of the cervix, and, as a result, to a decrease in the probability of conception, an increased risk of miscarriages, and also prevents natural delivery [3].

Laser vaporization

The use of aser technologies in the treatment of CIN plays an important role and is especially indicated for young patients with a verified diagnosis of CIN I – III, as well as when there are contraindications to the use of traditional methods of treatment or when patients refuse to use them.

One of these methods is LV, a treatment method based on the use of a focused laser beam with a diameter of up to 1 mm from a high-energy laser with a radiation power of up to 20 watts. LV is indicated for nulliparous women under the age of 40 with CIN II degree of pathological changes in the cervical epithelium. The main advantages of the method are the possibility of complete evaporation of the pathological focus, visual control of the depth of tissue destruction, and the absence of long-term edema and scar deformities, which allows for cervix integrity preservation and makes it possible to maintain its reproductive function [4].

Despite the low degree of injury and low rate of adverse reactions, the effectiveness of LV, according to various authors, varies from 50% to 98% [5,6,7,8,9].

J. A. Jordan presented the experience of treating 711 patients using the CO_2 LV method. During the follow-up period (20 months), the frequency of complete tumor regression (CTR) was 95% [5].

According to Fallani M. G. et al. (Department of Gynecology, University of Florence, Italy), the use of LV resulted in 97.5% CTR in 157 patients with CIN II – III [6]. The treatment of 94 patients with CIN III by LV, according to M. Fambini et al. (Department of Gynecology, University of Florence, Italy) resulted in CTR in 91.5% of cases. When partial regression or stabilization of the

pathological process was achieved, further treatment sessions were provided. In 32.7% of cases, an adverse reaction was noted in the form of moderate bleeding during the treatment session [7].

According to E. Saah-Briffaut (Clinique de Gynécologie, Hôpital Jeanne-de-Flandre, France), the use of LV in 52 patients with CIN II – III allowed to achieve CTR only in 67.3% of cases [8].

B. S. Yoon et al. (Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, South Korea) treated 141 CIN II patients with LV. The authors reported that the main factor determining the effectiveness of the method is the depth of ablation of pathological foci. The CTR rate was 90.1% [9].

At the same time, one can mention that ulceration, bleeding and secondary infection are observed among the adverse reactions that develop against the background of LV treatment. Another disadvantage is the method's inability to eliminate HPV, the virus which causes the development of CIN.

Photodynamic therapy

In connection with all the above, there is a need to search for new organ-preserving methods of CIN treatment. One of these methods is photodynamic therapy (PDT), a method based on the use of special substances referred to as photosensitizers (PS), which selectively accumulate in pathologically altered tissues. Subsequent exposure to laser radiation of a certain wavelength leads to the launch of a cascade of photochemical reactions, which result in the formation of a significant amount of free radicals and the initiation of oxidative stress syndrome in pathological tissues, leading to their death as a result of apoptosis and/or necrosis [10, 11, 12, 13, 14, 15, 16].

Important advantages of PDT in comparison with traditional methods of CIN treatment are the selectivity of exposure, the possibility of combining therapeutic and diagnostic options, the absence of the risk of serious adverse reactions which are typical for surgery, the relative cost-effectiveness of the method and the possibility of its repeated use.

The choice of a sparing and organ-preserving PDT method for young women with varying CIN stages is due to the desire to provide reliable treatment of patients and preserve their menstrual and reproductive functions, which is important for women planning pregnancy [17,18].

The use of PDT can not only effectively produce the desired effect on the pathological focus, but also leads to the eradication of HPV, thereby preventing a relapse. Currently, the world has accumulated considerable experience in the use of PDT with various photosensitizing agents (5-aminolevulinic acid (5-ALA), hematoporphyrin, photofrin II, chloride and its derivatives) in the treatment of patients with CIN.

Photodynamic therapy with 5-aminolevulinic acid

P. Hillemanns was among the first to use PDTs with the 5-ALA in application form (Department of Obstetrics and Gynecology, Ludwig-Maximilians-University, Germany) in the treatment of 10 patients with CIN II – III. Irradiation of pathological foci was performed 3–5 hours after local application of 10 ml of 20% solution of 5-ALA, the dose of light energy is 100 J/cm^2, the radiation power density is 100–150 mW/cm^2 (λ=635 nm). No serious adverse reactions were reported after the treatment. Several patients had moderate pain syndrom and vaginal discharge. The author reported that at the follow-up 3 months later, the frequency of CTR was 30% (n=3), and the remaining patients underwent cold-knife conization of the cervix due to insufficient effectiveness of the previous treatment [19].

A. Barnett et al. (School of Biomedical Sciences, University of Leeds, UK) reported poor PDT performance using 3% 5-ALA gel (Intrasite Gel®, Smith & Nephew Healthcare Ltd., Hull, UK) in 12 patients with CIN I – II included in a double-blind placebo-controlled randomized trial. 13 patients in the control group were treated with a gel that did not contain 5-ALA. Irradiation of pathological foci of the cervix was carried out 4 hours after local application of 3% 5-ALA gel, the dose of light energy being 100 J/cm^2, the radiation power density was 100 mW/cm^2 (λ=635 nm). There were no serious adverse reactions to the treatment, only 3 patients from the main group complained of discomfort and moderate pain during the PDT session. The CTR rate in the main group was 33%, whereas in the control group it was 31%. The authors did not reveal any statistically significant differences in the results of the treatment of patients in the comparison groups ($p>0.05$) [20].

K. A. Keefe et al. (Division of Gynecologic Oncology, Chao Family Compressive Cancer Center, USA) reported the results of phase I and II of the clinical trial of PDT tolerability and efficacy with the application form 5-ALA (200 mg/ml) in 40 patients with CIN II (n=16) and CIN III (n=24). The authors used an escalation of the light energy dose from 50 to 150 J/cm^2 (λ=630 nm), irradiation was carried out 1.5 hours after the application of 5-ALA to tissues with pathological changes. No serious adverse reactions to the treatment were observed, however, several patients mentioned discomfort and moderate pain during irradiation. Cytological and colposcopic control in 4 months after treatment resulted in CTR rate of 51%, in 8 months, a 46% rate, and 31% in 12 months. The authors concluded that the therapeutic effect did not depend of the light energy dose [21].

P. Soergel et al. (Department of Obstetrics and Gynecology, Hannover Medical School, Germany) reported on their experience of administering PDT treatment

with a gel form of hexaminolevulinate (thermogel) in 24 patients with CIN I – III. Irradiation of the cervix and cervical canal (λ=633 nm) was carried out 3–5 hours after gel application. No serious adverse events were observed after PDT. The follow-up after 6 months showed that CTR rate reached 63%. Patients had a long 6-month HPV remission: at CIN I-71%, CIN II-50% and CIN III-71% [22]. In the general group of patients (CIN I – III), the CTR rate was 67% [23].

In a literature review that included an analysis of the results of 14 clinical trials (472 patients with CIN I – III), K. N. Tao systematized the experience of using PDT with 5-ALA and porphyrinic PS agents [24]. The author reported that the CTR rate in the compared studies varied from 0 to 100%, and the effectiveness of HPV eradication was from 53.4 to 80% [25].

E. G. Novikova et al. (FSBI P. A. Hertsen MORC of the Ministry of Health of the Russian Federation) reported on the use of PDT with 20% 5-ALA ointment in 40 patients with primary cervical cancer after previous organ-preserving surgery (high cone-shaped amputation of the cervix). Irradiation was performed 6 hours after ointment application; a diode laser was used, its wavelength corresponding to 635 nm, the dose of light energy being 150 J/cm^2, and the radiation power density was 150–250 mW/cm^2. PDT of the cervical canal was performed with a flexible monofilament quartz light guide with a cylindrical diffuser providing a 360° light matrix, with the length of 1 cm corresponding to the length of the endocervix. Irradiation of the vaginal portion of the cervical stump was performed remotely via a light guide with a lens perpendicular to the organ and a spot diameter from 1.5 to 2.0 cm. No serious adverse events were observed. Complete eradication of HPV after one course of PDT of the cervical stump was achieved in 95% of cases, and in 5% of cases, after 2 courses of PDT [2].

Photodynamic therapy with the use of hematoporphyrin and its derivatives

The results of PDT with the use of ether polyaminopropyl (PHE) in the treatment of 31 patients with CIN II – III were published by H. Ichimura et al. (Department of Obstetrics and Gynecology, Hyogo Medical Center for Adults, Japan). Irradiation was performed 60 h after intravenous infusion of PS at a dose of 2 mg/kg of body weight, with a wavelength of 630 nm, a dose of light energy of 100 J/cm^2. No serious adverse events were observed. The CTR rate recorded during morphological examination 3 months after PDT was 90%, while the share of HPV-negative patients was 76%. The follow-up after 12 months showed that CTR rate reached 100% [26].

Two years later, Yamaguchi S. et al. (Departments of Gynecology and Pathology, Osaka City General Hospital, Japan) presented data on successful PDT treatment with intravenous Photofrin administered at a dose of 2 mg/kg body weight in 105 patients with CIN I – III. Irradiation, as in the previous study, was performed with a wavelength of 630 nm, and the light energy dose of 100 J/cm^2. CTR rate 3 months after the treatment was 90%. The percentage of HPV-negative patients at the follow-up at 3, 6 and 12 months after treatment was 75%, 74% and 72%, respectively. However, it is worth noting the high frequency of adverse reactions: moderate phototoxicity was recorded in 50 (48%) of 105 patients [27].

M. C. Choi et al. (Department of Obstetrics and Gynecology, Comprehensive Gynecologic Cancer Center, South Korea) investigated the effectiveness of PDT in combination with electrosurgical excision and cervical conization in 73 patients with CIN II – III [28]. Irradiation was performed 48 hours after intravenous administration of porphyrin-type PS (Photofrin) at a dose of 2 mg/kg of body weight, using a laser with a wavelength of 630 nm. The frequency of CTR during the 12-month follow-up period was 98.1%. HPV eradication was achieved in 89.8% and 87%, respectively, at the follow-up 3 months and 12 months after PDT. The frequency of adverse reactions in the form of cutaneous phototoxicity and cervical canal stenosis was 13.6%.

C. H. Jeong compared the effectiveness of PDT with intravenous Photohem administration at a dose of 2 mg/kg body weight and diathermoelectroconization in 2 groups of patients with CIN II–III. Each group included 48 patients. The CTR rate was 93% and 95%, respectively, and HPV was not detected in 84% and 82% of cases. The author came to the conclusion that PDT can be used as an alternative method for selective destruction of pathological tissues, which allows for preserving women's fertility after treatment [29].

Y. K. Park et al. (Department of Obstetrics and Gynecology, Dankook University College of Medicine, South Korea) presented the experience of PDT treatment of 19 CIN II – III patients with the use of an injectable form of Photohem (2 mg/kg body weight) and Photofrin II (2 mg/kg body weight). Irradiation was performed 48 hours after the introduction of PS at a wavelength of 630 nm and a dose of light energy of 240 J/cm^2. The adverse reactions reported by the authors included skin phototoxicity and moderate pain during the PDT session. The CTR rate was 91% [30].

Photodynamic therapy with chlorin-type photosensitizers

Belarusian researchers (the National Cancer Center of the Republic of Belarus) presented their experience of PDT with an injectable form of Photolon, a chlorine PS, in 112 patients with CIN II–III [31]. Irradiation of the cervix and cervical canal was performed with light energy doses from 100 to 150 J/cm^2 (λ=660±5 nm), 2.5–

Таблица
Опыт применения ФДТ с различными ФС в лечении пациенток с CIN
Table
Experience of using PDT with various PS in the treatment of patients with CIN

Автор, год исследования Author, year of research	Диагноз, число пациентов Diagnosis, number of patients	ФС PS	Параметры облучения Photoirradiation parameters	Частота полной регрессии (ПР) Percentage of complete regressions (CR)	Частота элиминации ВПЧ Percentage of complete HPV eliminations
5-АЛК и ее производные (аппликационная форма) *5-ALA and its derivatives (application form)*					
Hillemanns P., 1999 [19]	CIN II-III, n=10	20% раствор 5-АЛК	100 Дж/см^2 100–150 мВт/см^2 λ=635 нм	30%	
	CIN II-III, n=10	20% solution 5-ALA	100 J/cm^2 100–150 мW/см^2 λ=635 nm	30%	
Barnett A., 2003 [20]	CIN I-II, n=25 12 – с ФДТ 13 – без ФДТ	3% раствор 5-АЛК (в Intrasite Gel®)	100 Дж/см^2 100 мВт/см^2 λ=635 нм	с ФДТ – 33% без ФДТ – 31%	
	CIN I-II, n=25 12 – with PDT 13 – without PDT	3% solution 5-ALA (in Intrasite Gel®)	100 J/cm^2 100 mW/cm^2 λ=635 nm	with PDT – 33% without PDT – 31%	
Keefe K.A., 2002 [21]	CIN II (n=16) CIN III (n=24)	20% раствор 5-АЛК	50–150 Дж/см^2 0,8 Вт/см^2 λ=630 нм	частота ПР: ч/з 4 мес – 51%; ч/з 8 мес – 46%; ч/з 12 мес – 31%	
	CIN II (n=16) CIN III (n=24)	20% solution 5-ALA	50–150 J/см^2 0,8 W/cm^2 λ=630 nm	CR rate: thr. 4 mon. – 51%; thr. 8 mon. – 46%; thr. 12 mon. – 31%;	
Soergel P., 2008 [22]	CIN I (n=7) CIN II (n=10) CIN III (n=7)	гексамино-левулинат термогель 10 mM	λ=633 нм	63%	71%; 50%; 71%
	CIN I (n=7) CIN II (n=10) CIN III (n=7)	hexamino-levulinate thermogel 10 mM	λ=633 nm	63%	71%; 50%; 71%
Гематопорфирин и его производные (инъекционная форма) *Hematoporphyrin and its derivatives (injectable form)*					
Ichimura H., 2003 [26]	CIN II (n=2) CIN III (n=29)	полигемато-порфирин эфир, 2 mg/kg	100 Дж/см^2 λ=630 нм	ч/з 3 мес – 90%; ч/з 12 мес – 100%.	76%
	CIN II (n=2) CIN III (n=29)	polyhemato-porphyrin ether, 2 mg/kg	100 J/cm^2 λ=630 nm	thr. 3 mon. – 90%; thr. 12 mon – 100%	76%
Yamaguchi S, 2005 [27]	CIN I-III, n=105	фотофрин, 2 мг/кг	100 Дж/см^2 λ=630 нм	90%.	3–12 мес – 72–75%
	CIN I-III, n=105	photofrin, 2 mg/kg	100 J/cm^2 λ=630 nm	90%	thr.3–12 mon – 72–75%
Choi M.C., 2013 [28]	CIN II-III, n=73	фотофрин, 2 мг/кг	100 Дж/см^2 λ=630 нм	98,1%.	ч/з 3 мес – 89,8%; ч/з 12 мес – 87%
	CIN II-III, n=73	photofrin, 2 mg/kg	100 J/cm^2 λ=630 nm	98,1%	thr. 3 mon. – 89,8%; thr. 12 mon. – 87%

Автор, год исследования Author, year of research	Диагноз, число пациентов Diagnosis, number of patients	ФС PS	Параметры облучения Photoirradiation parameters	Частота полной регрессии (ПР) Percentage of complete regressions (CR)	Частота элиминации ВПЧ Percentage of complete HPV eliminations
Jeong C.H., 2015 [29]	CIN II-III, n=48 CIN II-III, n=48	фотогем, 2 мг/кг photogem, 2 mg/kg	>200 Дж/см^2 λ=630 нм >200 J/cm^2 λ=630 nm	CIN II – 93% CIN III – 95% CIN II – 93% CIN III – 95%	CIN II – 84% CIN III – 82% CIN II – 84% CIN III – 82%
Park Y.K., 2016 [30]	CIN II-III, n=23 CIN II-III, n=23	фотогем 2 мг/кг (n=2), фотофрин, 2 мг/кг photogem 2 mg/kg (n=2), photofrin 2 mg/kg	240 Дж/см^2 0,4 Вт, λ_1=632 нм, λ_2=630 нм 240 J/cm^2 0,4 W, λ_1=632 nm, λ_2=630 nm	91% 91%	
Хлорин и его производные (инъекционная форма) *Chlorin and its derivatives (injectable form)*					
Istomin Yu.P., 2010 [31]	CIN II-III, n=112 CIN II-III, n=112	фотолон, 2–2,5 мг/кг photolon 2–2,5 mg/kg	100–150 Дж/см^2 0,5–0,6 Вт, λ=660±5 нм 100–150 J/cm^2 0,5–0,6 W, λ=660±5 nm	92,8% 92.8%	53,4% (у 47 из 88) 53.4% (47 out of 88)
Отдельнова О.Б., 2008 [33] Otdelnova O.B., 2008 [33]	фоновые и предраковые заболевания шейки матки, n=72 pre-existing and precancerous diseases of the cervix, n=72	фотодитазин (0,5% гель и/или 0,5 мг/кг) fotoditazin (0.5% gel or 0.5 mg/kg)	80–250 Дж/см^2, λ=662 нм 80–250 J/cm^2, λ=662 nm	88,9% 88.9%	
Гребенкина Е.В., 2014 [34] Grebenkina E.V., 2014 [34]	CIN III (n=8), cancer in situ (n=4) CIN III (n=8), cancer in situ (n=4)	фотолон, 0,75–1,15 мг/кг photolon, 0,75–1,15 mg/kg	150 Дж/см^2 400–500 мВт/см^2 λ=660 нм 150 J/cm^2 400–500 mW/cm^2 λ=660 nm	у 4 пациенток эффект оценен как ПР, у 7 обнаружена CIN I, у 1 – CIN II. in 4 patients, the effect was assessed as CR, in 7 patients CIN I was found, in 1 – CIN II.	80% 80%
Филоненко Е.В., 2015 [35] Filonenko E.V., 2015 [35]	CIN II (n=5) CIN III (n=13) CIN II (n=5) CIN III (n=13)	радахлорин, 1 мг/кг radachlorin, 1 mg/kg	300–350 Дж/см^2, λ=662 нм 300–350 J/cm^2, λ=662 nm	CIN II – 100% CIN III – 77% CIN II -100% CIN III – 77%	
Никонов С.Д., 2019 [36] Nikonov S.D., 2019 [36]	CIN III, cancer in situ n=43 CIN III, cancer in situ n=43	фотодитазин, радахлорин, 1 мг/кг fotoditazin, radachlorin, 1 mg/kg	0,4 Вт, λ=662 нм 0,4 W, λ=662 nm	95,35% 95.35%	

3.0 hours after the end of the PS infusion. At the first stage, the vaginal part of the cervix was remotely irradiated with a fiber-optic light guide with a microlens. When the size of the CIN focus did not exceed 3 cm, irradiation was performed with a single field with a diameter of 4 cm. If the size of the pathological focus exceeded 3 cm, 4 fields with a diameter of 2.0 to 2.5 cm were irradiated. At the second stage, the entire length of the cervical canal was irradiated with a fiber-optic catheter which had a cylindrical diffuser. There were no serious adverse reactions to the treatment; however, several patients showed discomfort, moderate pain during irradiation, and vaginal discharge. According to the authors, the CTR rate detected 3 months after treatment was 92.8%, and complete HPV eradication was observed in 53.4% of cases.

In a later study, the authors summarized the experience of PDT use in patients with CIN II (n=230) and CIN III (n=378) treated between 2006 and 2019. Follow-up observations for a period of 3 months or more found only occasional cases of cervical canal stenosis and coagulated cervix syndrome. The CTR rate determined in 2.5–3.0 months after PDT in the group of patients with CIN II reached 100%, with CIN III, 94.1% [32].

O. B. Otdelnova et al. (N. I. Pirogov Russian State Medical University, Department of Obstetrics and Gynecology, Russian Federation) presented the results of PDT treatment of 72 patients with background and precancerous diseases of the cervix. The photosensitizing agent was Photoditazine, in application (0.5% gel) and injection (0.5 mg/kg body weight) forms. Irradiation of the cervix and cervical canal was performed 1.5–2.0 hours after the introduction of PS (λ=662 nm). Depending on the nature of the pathological process, the duration of exposure varied from 15 to 40 minutes, and the dose of light energy from 80 to 250 J/cm$^{2.}$ The control group used for comparison was administered diathermosurgical treatment (diathermocoagulation and diathermoconization) with the ES 500 M device (Russia). There were no serious adverse reactions after PDT, and side effects in the form of incomplete cervical epithelization were observed in 8 (11.1%) patients. In the control group, 76.6% of patients suffered from pain in the lower abdomen, 6.7% of patients had bleeding in the postoperative period, 6.7% had exacerbation of chronic salpingoophoritis, 30% had colpitis, 20% had incomplete epithelialization of the cervix. With the use of PDT, the CTR rate was 88.9%, which was confirmed by the results of colposcopy and cytological tests [33].

E. V. Grebenkina et al. (Nizhny Novgorod Regional Cancer Dispensary, Russian Federation) presented the results of PDT in 8 patients with CIN III and 4 patients with cancer in situ. Photolon was administered intravenously at a dose of 0.75–1.15 mg/kg of body weight. After 1.5–2.0 hours, an irradiation session was performed with a light energy dose of 150 J/cm$^{2.}$ Laser radiation was delivered to the endocervix with quartz light guides with 3 cm long cylindrical diffusers providing a 360° light matrix, and a macro lens with a light spot from 1 to 2 cm in diameter was applied to the vaginal portion of the cervix. 30 days after treatment, cervical conization was performed with cervical canal curettage, and the results of PDT were evaluated. During PDT, no serious adverse reactions were registered, the irradiation session was well tolerated, and only 2 patients had pain syndrome (pain in the lower abdomen) during the PDT session. According to the histological study of postoperative material, the effect of treatment in 4 patients was estimated as CTR, CIN I was detected in 7 patients, and CIN II in one. HPV eradication was achieved in 80% of cases [34].

E. V. Filonenko et al. published the results of phase III clinical trials of Radachlorin use in PDT in 30 patients with precancerous diseases and initial cervical cancer: ectopia – 4 cases, CIN II – 5 cases, CIN III – 13 cases, carcinoma in situ – 4 cases, stage Ia of cervical cancer – 4 cases. PS was administered once, intravenously at a dose of 1 mg per kilo of body weight 3 hours before irradiation, and light energy doses from 300 to 350 J/cm^2 (λ = 662 nm) were used. The PDT session of the cervical canal was performed via a quartz light guide with a cylindrical diffuser from 1 to 3 cm long along the entire length of the cervical canal, and the vaginal part of the cervix was irradiated via a macro lens with a light spot diameter from 2 to 3 cm, depending on the anatomical characteristics of the organ. No serious adverse events were observed after PDT. The CTR rate in patients with CIN II and III was 100% and 77%, respectively [35].

S. D. Nikonov et al. (FBHI "Primorsky Regional Cancer Dispensary", Russian Federation) in their study evaluated the effectiveness of PDT HPV-associated CIN III and carcinoma in situ in 43 nulliparous patients who refused to undergo conization. Injectable forms of photoditazine (1 mg/kg body weight) and radachlorine (1 mg/kg body weight) with an exposure of 3 hours were used as PS. Irradiation was performed with Lakhta-Milon and Latus lasers (λ=662 nm). Exocervix PDT was performed remotely, monopositionally, via a light guide with a collimator at a radiation power of 2 W and a light spot diameter of 4 cm. PDT of the cervical canal was performed via a light guide with a cylindrical diffuser 4 cm long with a radiation power of 0.4 W. Complete recovery was observed in 95.35% of cases, and in the subgroup of nulliparous patients, in 96.3% (n=26), which was confirmed by the elimination of all types and combinations of HPV, as well as a successful colposcopic and cytological picture [36].

To summarize the above data on the effectiveness of PDT in various research centers and clinics in the CIS, Europe, Southeast Asia, and the United States, the data

on the effectiveness of PDT in various studies are summarized in the table.

Conclusion

Thus, the effectiveness of PDT in the treatment of patients with CIN depends on the PS chemical structure and the method of its administration. In most cases, the highest efficiency is achieved with systemic (intravenous) administration of PS [2, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30], while the use of 5-ALA application forms (solutions, gels and ointments) does not lead to a high CTR rate [14, 15, 16, 17, 18]. The above results of studies conducted by various authors confirm the ample opportunities of PDT use in the treatment of patients with CIN, which is possible due to the fact that this method has a number of advantages compared to the existing standard methods of treatment.

The main advantages of PDT include:

- minimal toxicity to surrounding normal tissues, due to selective accumulation of PS in pathological tissues;
- low risk of severe pain syndrome;
- negligible system effects;
- lack of primary and acquired resistance mechanisms;
- possibility of administering treatment sessions on outpatient basis;
- possibility of combination with other treatment methods;
- the absence of limiting cumulative doses of PS and light exposure, the possibility to repeat the treatment;
- good cosmetic results;
- organ-sparing approach.

REFERENCES

1. Santesso N., Mustafa R.A., Wiercioch W. et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia, *Int. J. Gynecol. Obst*, 2016, vol. 132, pp. 266–271.
2. Novikova E.G., Trushina O.I. Photodynamic therapy in the prevention of human papillomavirus (HPV) - associated recurrence of cervical cancer, *Oncogynecology*, 2015, No. 2, pp. 25–31. (in Russ.)
3. Laptsevich T.P., Istomin Yu.P., Chalov V.N. Photodynamic therapy with a photolon of cervical intraepithelial neoplasia II-III degree, *Laser medicine*, 2009, vol. 13(3), pp. 30–35. (in Russ.)
4. Laptsevich T.P., Istomin Yu.P., Chalov V.N. Photodynamic therapy of cervical intraepithelial neoplasia, *LAP LAMBERT Academic Publishing GmbH,* 2011, p. 109. (in Russ.)
5. Jordan J.A., Woodman C.B., Mylotte M.J. et al. The treatment of cervical intraepithelial neoplasia by laser vaporization, *Br. J. Obstet. Gynaecol,* 1985, vol. 92(4), pp. 394–398.
6. Fallani M.G. Laser CO2 vaporization for high-grade intraepithelial neoplasia: a long-term follow-up series, *Gynecol. Oncol*, 2003, vol. 91(1), pp. 130–133.
7. Fambrini M., Penna C., Pieralli A. et al. CO2 laser cylindrical excision or standard re-conization for persistent-recurrent high-grade cervical intraepithelial neoplasia (HG-CIN) in women of fertile age, *Anticancer Res*, 2008, vol. 28(6), pp. 3871–3875.
8. Saah-Briffaut E., Collinet P., Saah R. et al. Treatment of squamous intraepithelial lesion of type CIN2 et CIN3 with laser CO2 vaporization: retrospective study of 52 cases, *J. Gynecol. Obstet. Biol. Reprod (Paris)*, 2006, vol. 35(8), pp. 785–789.
9. Yoon B.S., Seong S.J., Song T. et al. Risk factors for treatment failure of CO2 laser vaporization in cervical intraepithelial neoplasia 2, *Arch. Gynecol. Obst*, 2014, vol. 290(1), pp. 115–119.
10. Abdel-Kader M.H. Photodynamic therapy. From theory to application, *Verlag, Berlin, Heidelberg* : Springer, 2014, p. 312.
11. Dougherty T.J., Gomer C.J., Henderson B.W. Photodynamic therapy, *J. Natl. Cancer Inst*, 1998, vol. 90(12), pp. 889–905.
12. Agostinis P., Berg K., Cengel K.A. Photodynamic therapy of cancer: an update. *CA: A Cancer J. Clin*, 2011, vol. 61, pp. 250–281.
13. Sokolov, V.V., Chissov, V.I., Filonenko, E.V. et al. Photodynamic therapy of cancer with the photosensitizer PHOTOGEM, *Proceedings of SPIE - The International Society for Optical Engineering*, 1995, vol. 2325, pp. 367–374.

ЛИТЕРАТУРА

1. Santesso N., Mustafa R.A., Wiercioch W. et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. // Int. J. Gynecol. Obst. – 2016. – Vol. 132. – P. 266–271.
2. Новикова Е.Г., Трушина О.И. Фотодинамическая терапия в профилактике ВПЧ-ассоциированных рецидивов рака шейки матки // Онкогинекология. – 2015. – № 2. – С. 25–31.
3. Лапцевич Т.П., Истомин Ю.П., Чалов В.Н. Фотодинамическая терапия с фотолоном цервикальной интраэпителиальной неоплазии II-III степени // Лазерная медицина. – 2009. – Т. 13, вып. 3. – С. 30–35.
4. Лапцевич Т.П., Истомин Ю.П., Чалов В.Н. Фотодинамическая терапия цервикальной интраэпителиальной неоплазии // LAP LAMBERT Academic Publishing GmbH. – 2011. – p .109.
5. Jordan J.A., Woodman C.B., Mylotte M.J. et al. The treatment of cervical intraepithelial neoplasia by laser vaporization // Br. J. Obstet. Gynaecol. – 1985. – Vol. 92(4). – P. 394–398.
6. Fallani M.G. Laser CO_2 vaporization for high-grade intraepithelial neoplasia: a long-term follow-up series // Gynecol. Oncol. – 2003. – Vol. 91(1). – P. 130–133.
7. Fambrini M., Penna C., Pieralli A. et al. CO_2 laser cylindrical excision or standard re-conization for persistent-recurrent high-grade cervical intraepithelial neoplasia (HG-CIN) in women of fertile age // Anticancer Res. – 2008. – Vol. 28(6). – P. 3871–3875.
8. Saah-Briffaut E., Collinet P., Saah R. et al. Treatment of squamous intraepithelial lesion of type CIN2 et CIN3 with laser CO2 vaporization: retrospective study of 52 cases // J. Gynecol. Obstet. Biol. Reprod (Paris). – 2006. – Vol. 35(8). – P. 785–789.
9. Yoon B.S., Seong S.J., Song T. et al. Risk factors for treatment failure of CO_2 laser vaporization in cervical intraepithelial neoplasia 2 // Arch. Gynecol. Obst. – 2014. – Vol. 290(1). – P. 115–119.
10. Abdel-Kader M.H. Photodynamic therapy. From theory to application // Verlag, Berlin, Heidelberg : Springer, 2014. – P. 312.
11. Dougherty T.J., Gomer C.J., Henderson B.W. Photodynamic therapy // J. Natl. Cancer Inst. – 1998. – Vol. 90(12). – P. 889–905.
12. Agostinis P., Berg K., Cengel K.A. Photodynamic therapy of cancer: an update // CA: A Cancer J. Clin. – 2011. – Vol. 61. – P. 250–281.
13. Sokolov, V.V., Chissov, V.I., Filonenko, E.V. et al. Photodynamic therapy of cancer with the photosensitizer PHOTOGEM // Proceedings of SPIE - The International Society for Optical Engineering. – 1995. – Vol. 2325. – P. 367–374.

14. 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.
15. Yakubovskaya, R.I., Morozova N.B., Pankratov A.A., et al. Experimental photodynamic therapy: 15 years of development, *Russian Journal of General Chemistry*, 2015, vol. 85(1), pp. 217 – 239.
16. Petrishchev N.N., Galkin M.A., Grishacheva T.G., et al. The effect of chlorin e6 drug on platelet aggregation activity, *Biomedical Photonics*, 2019, vol. 8(3), pp. 4–10. (In Russ.) https://doi.org/10.24931/2413–9432–2019–8-3–4-10
17. Laptsevich T.P., Istomin Yu.P., Chalov V.N. Methods of treatment of cervical intraepithelial neoplasias: reality and prospects, *Medical news*, 2008, No.9, pp. 10–16. (in Russ.)
18. Larkin A.I., Trukhanov K.A. Operational analysis of complex medical states by photonics methods, *Biomedical Photonics,* 2018, vol. 7(1), pp. 28–31. (In Russ.) https://doi.org/10.24931/2413–9432–2018–7-1–28–31
19. Hillemanns P, Korell M, Schmitt-Sody M, Baumgartner R. et al. Photodynamic therapy in women with cervical intraepithelial neoplasia using topically applied 5-aminolevulinic acid, *Int. J. Cancer*, 1999, vol. 81(1), pp. 34–38.
20. Barnett A.A., Haller J.C., Cairnduff F. et al. A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia, *Int. J. Cancer*, 2003, vol. 103(6), pp. 829–832.
21. Keefe K.A., Tadir Y., Tromberg B. et al. Photodynamic therapy of high-grade cervical intraepithelial neoplasia with 5-aminolevulinic acid, *Lasers Surg. Med*, 2002, vol. 31(4), pp. 289–293.
22. Soergel P., Wang X., Stepp H. et al. Photodynamic therapy of cervical intraepithelial neoplasia with hexaminolevulinate, *Lasers Surg. Med*, 2008, vol. 40(9), pp. 611–615.
23. Soergel P., Dahl G.P., Onsrud M. et al. Photodynamic therapy of cervical intraepithelial neoplasia 1–3 and human papilloma virus (HPV) infection with methylaminolevulinate and hexaminolevulinate – A double-blind, dose-finding study, *Lasers Surg. Med*, 2012, vol. 44(6), pp. 468–474.
24. Yakubovskaya R.I., Pankratov A.A., Filonenko E.V. et al. Comparative experimental study of 5-ALA and 5-ALA hexyl ester specific activity, *Biomedical Photonics*, 2018, vol. 7(3), pp. 43–46. (In Russ.) https://doi.org/10.24931/2413–9432–2018–7-3–43–46
25. Tao X.H., Guan Y., Shao D. et al. Efficacy and safety of photodynamic therapy for cervical intraepithelial neoplasia: a systemic review, *Photodiagnosis Photodyn. Ther*, 2014, vol. 11(2), pp. 104–112.
26. Ichimura H., Yamaguchi S., Kojima A. et al. Eradication and reinfection of human papillomavirus after photodynamic therapy for cervical intraepithelial neoplasia, *Int. J. Clin. Oncol*, 2003, vol. 8(5), pp. 322–325.
27. Yamaguchi S., Tsuda H., Takemori M. et al. Photodynamic therapy for cervical intraepithelial neoplasia, *Oncology*, 2005, vol. 69, pp. 110–116.
28. Choi M.C., Jung S.J., Park H. et al. Photodynamic therapy for management of cervical intraepithelial neoplasia II and III in young patients and obstetric outcomes, *Lasers Surg. Med*, 2013, vol. 45(9), pp. 564–572.
29. Jeong C.H. 10th World Congress of the International Photodynamic Association, *Munich, Germany*, 2005, p.14.
30. Park Y.K., Park C.H. Clinical efficacy of photodynamic therapy, *Obstet. Gynecol. Sci*, 2016, vol. 59(6), pp. 479–488.
31. Istomin Yu.P., Lapzevich T.P., Chalau V.N. et al. Photodynamic therapy of cervical intraepithelial neoplasia grades II and III with Photolon, *Photodiagnosis Photodyn. Ther*, 2010, vol. 7(3), pp. 144–151.
32. Tserkovskiy D.A., Artemieva T.P. Photodynamic therapy of cervical intraepithelial neoplasia, *Evrazijskij onkologicheskij zhurnal*, 2020, vol. 8, No. 2 (Appendix), p. 355. (in Russ.)

14. 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.
15. Yakubovskaya, R.I., Morozova N.B., Pankratov A.A. et al. Experimental photodynamic therapy: 15 years of development // Russian Journal of General Chemistry. – 2015. – Vol. 85(1). – P. 217 – 239.
16. Петрищев Н.Н., Галкин М.А., Гришачева Т.Г., Дементьева И.Н., Чефу С.Г. Влияние препарата на основе хлорина е6 на агрегационную активность тромбоцитов // Biomedical Photonics. – 2019. – Т.8, №3. – С. 4–10. https://doi.org/10.24931/2413–9432–2019–8-3–4-10
17. Лапцевич Т.П., Истомин Ю.П., Чалов В.Н. Методы лечения цервикальных интраэпителиальных неоплазий: реальность и перспективы // Медицинские новости. – 2008. – № 9. – С. 10–16.
18. Ларкин А.И., Труханов К.А. Оперативный анализ сложных медицинских состояний методами фотоники // Biomedical Photonics. – 2018. – Т.7, №1. – С.28–31. https://doi.org/10.24931/2413–9432–2018–7-1–28–31
19. Hillemanns P, Korell M, Schmitt-Sody M, Baumgartner R. et al. Photodynamic therapy in women with cervical intraepithelial neoplasia using topically applied 5-aminolevulinic acid // Int. J. Cancer. – 1999. – Vol. 81(1). – P. 34–38.
20. Barnett A.A., Haller J.C., Cairnduff F. et al. A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia // Int. J. Cancer. – 2003. – Vol. 103(6). – P. 829–832.
21. Keefe K.A., Tadir Y., Tromberg B. et al. Photodynamic therapy of high-grade cervical intraepithelial neoplasia with 5-aminolevulinic acid // Lasers Surg. Med. – 2002. – Vol. 31(4). – P. 289–293.
22. Soergel P., Wang X., Stepp H. et al. Photodynamic therapy of cervical intraepithelial neoplasia with hexaminolevulinate // Lasers Surg. Med. – 2008. – Vol. 40(9). – P. 611–615.
23. Soergel P., Dahl G.P., Onsrud M. et al. Photodynamic therapy of cervical intraepithelial neoplasia 1–3 and human papilloma virus (HPV) infection with methylaminolevulinate and hexaminolevulinate – A double-blind, dose-finding study // Lasers Surg. Med. – 2012. – Vol. 44(6). – P. 468–474.
24. Якубовская Р.И., Панкратов А.А., Филоненко Е.В., Лукьянец Е.А., Иванова-Радкевич В.И., Трушин А.А., Каприн А.Д. Сравнительное экспериментальное исследование специфической активности 5-АЛК и гексилового эфира 5-АЛК // Biomedical Photonics. – 2018. – Т.7, № 3. – С. 43–46.
25. Tao X.H., Guan Y., Shao D. et al. Efficacy and safety of photodynamic therapy for cervical intraepithelial neoplasia: a systemic review // Photodiagnosis Photodyn. Ther. – 2014. – Vol. 11(2). – P. 104–112.
26. Ichimura H., Yamaguchi S., Kojima A. et al. Eradication and reinfection of human papillomavirus after photodynamic therapy for cervical intraepithelial neoplasia // Int. J. Clin. Oncol. – 2003. – Vol. 8(5). – P. 322–325.
27. Yamaguchi S., Tsuda H., Takemori M. et al. Photodynamic therapy for cervical intraepithelial neoplasia // Oncology. – 2005. – Vol. 69. – P. 110–116.
28. Choi M.C., Jung S.J., Park H. et al. Photodynamic therapy for management of cervical intraepithelial neoplasia II and III in young patients and obstetric outcomes // Lasers Surg. Med. – 2013. – Vol. 45(9). – P. 564–572.
29. Jeong C.H. 10th World Congress of the International Photodynamic Association // Munich, Germany. – 2005. – P.14.
30. Park Y.K., Park C.H. Clinical efficacy of photodynamic therapy // Obstet. Gynecol. Sci. – 2016. – Vol. 59(6). – P. 479–488.
31. Istomin Yu.P., Lapzevich T.P., Chalau V.N. et al. Photodynamic therapy of cervical intraepithelial neoplasia grades II and III with Photolon® // Photodiagnosis Photodyn. Ther. – 2010. – Vol. 7(3). – P. 144–151.

33. Otdelnova O.B., Khashukoeva A.Z., Ibragimova M.I. Possibilities of photodynamic therapy using Fotoditazin photosensitizer in the treatment of gynecological diseases, *Ross. bioter. zhurnal*, 2008, vol. 7 (4), pp. 47–52. (in Russ.)
34. Grebenkina E.V., Gamayunov S.V., Kuznetsov S.S. et al. Photodynamic therapy of diseases of the cervix, *Fotodinamicheskaya terapiya i fotodiagnostika*, 2014, No.2, pp. 12–14. (in Russ.)
35. Filonenko E.V., Serova L.G., Ivanova-Radkevich V.I. Results from phase III clinical trials with radachlorine for photodynamic therapy of pre-cancer and early cancer of cervix, *Biomedical Photonics,* 2015, vol.4 (3), pp.36–42. (In Russ.) https://doi.org/10.24931/2413–9432–2015–4-3–36–42
36. Nikonov S.D., Pasman M.N., Korotin D.A. PDT of HPV-associated cervical intraepithelial neoplasia of the third degree (CIN III) - an alternative to the refusal of nulliparous women from cervical conization, *Lazernaya meditsina*, 2019, vol. 23 (3), p. 39. (in Russ.)

32. Церковский Д.А., Артемьева Т.П. Фотодинамическая терапия цервикальной интраэпителиальной неоплазии // Евразийский онкологический журнал. – 2020. – Т. 8, № 2 (Приложение). – С. 355.
33. Отдельнова О.Б., Хашукоева А.З., Ибрагимова М.И. Возможности фотодинамической терапии с использованием фотосенсибилизатора фотодитазин в лечении гинекологических заболеваний // Росс. биотер. журнал. – 2008. – Т. 7, № 4. – С. 47–52.
34. Гребенкина Е.В., Гамаюнов С.В., Кузнецов С.С. и др. Фотодинамическая терапия заболеваний шейки матки // Фотодинамическая терапия и фотодиагностика. – 2014. – № 2. – С. 12–14.
35. Филоненко Е.В., Серова Л.Г., Иванова-Радкевич В.И. Результаты III фазы клинических исследований препарата радахлорин для фотодинамической терапии предрака и начального рака шейки матки // Biomedical Photonics. – 2015. – Т. 4, № 3. – С. 36–42.
36. Никонов С.Д., Пасман М.Н., Коротин Д.А. ФДТ ВПЧ-ассоциированной цервикальной интраэпителиальной неоплазии III степени (CIN III) – альтернатива при отказе нерожавших женщин от конизации шейки матки // Лазерная медицина. – 2019. – Т. 23, № 3. – С. 39.