

Photodynamic Therapy For Vulvar Carcinoma In Situ (Case Report)

ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

The article presents a clinical case of the successful application of photodynamic therapy with photosensitizer photon in a patient with vulvar cancer in situ. The use of an exposure dose of light of 100 J/cm² made it possible to achieve complete clinical and morphological regression of the pathological focus, confirmed by control observations at 1, 3 and 6 months.

Keywords: vulvar cancer in situ, photodynamic therapy, photosensitizer, photolon.

1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

~~Despite~~ its visual diagnostic availability, vulvar cancer is one of the most difficult to treat malignant tumors in the reproductive system of women. This is due to the peculiarities of blood supply, innervation and lymphatic outflow, as well as topographical proximity of adjacent organs, as well as to the high psychosexual and physiological significance of the woman's external genitalia for her normal life [1].

Vulvar cancer is a rare disease and accounts for 2-5% of malignant tumors of female genital organs. In 50% of cases, vulvar carcinomas occurs at the age of 60 or more years, although in recent years there has been an increase in the incidence among young women. This fact is associated with an increase in the incidence of infection of women with human papillomavirus and herpes. Most vulvar carcinomas affect the large labia (52%). The second most frequent localization of cancer of the external genitalia is the clitoris (12-20%). The pathological process in the labia minora is found in 7.1% of patients, in the posterior spike — in 6.4%, in the periurethral zone in 1.7%, in the bartholin gland in 0.2% [2].

The main clinical symptoms of vulvar cancer are:

1. irritation;
2. persistent and intensifying pruritus of the vulva;
3. presence of a tumor in the form of a wart or abrasion of a red or white color;
4. painful ulcer that has not healed for more than a month;
5. pain in the vulva, bearing a long recurrent and persistent nature.

According to the Clinical Recommendations of the Association of Russian Oncologists for the Diagnosis and Treatment of Patients with vulvar cancer in situ (T_{is}N₀M₀, stage 0, preinvasive carcinoma), conventional therapies are [3]:

1. wide local excision at a distance of 0.5-1 cm from the edge of the tumor;
2. CO₂ laser ablation;
3. CO₂ laser ablation in combination with surgical intervention;
4. simple (cutaneous) vulvectomy with or without tissue graft transplantation;
5. chemotherapy with application form of 5-fluorouracil (5% ointment).

~~As our opinion, photodynamic therapy is a~~ promising method of treatment of vulvar cancer in situ. PDT is a relatively therapeutic modality for neoplastic diseases, which involves light activation, in the presence of molecular oxygen, of certain dyes (photosensitizers) that have been somewhat selectively taken up by the target tissue. The two possible mechanisms might be: a) promoting mitochondria to release **Cyto-C and activate Caspase-3**, then to initiate **apoptosis**; b) the destroying of microvessels, **inhibition of angiogenesis** and the induction of ischemia and anoxia of tumor cells, resulting in ischemic necrosis [4, 5, 6].

We present a case report that illustrates the antitumor efficacy of photodynamic therapy in patients with vulvar cancer in situ]

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

[The work is based on the analysis of treatment results of patient T., 54 years old (4736/2013) with vulvar cancer in situ who received treatment in Department of Hyperthermia and photodynamic therapy N.N. Alexandrov National Cancer Centre of Belarus. The treatment procedure was approved by local ethic committee. Patient signed informed consent to PDT in compliance with Helsinki declaration of 1964 (revised 2013).

The patient asked for medical help herself with complaints about the presence of a spot in the area of the external genitalia. After an additional examination in 2013, the vulvar cancer is suspected. Histological examination (October 2013) revealed the presence of vulvar cancer cells in situ. A clinical diagnosis was established: vulvar cancer in situ, T_{is}N₀M₀, stage 0.

In connection with the localization of the tumor process, the patient was offered organ-preserving treatment with photodynamic therapy. Photosensitizer «Photolon» (RUE «Belmedpreparaty», Republic of Belarus) was injected intravenously at a dose of 2.4 mg/kg (200 mg) body weight, in a darkened room. The tumor photoirradiation session was carried out 3 hours after the injection of Photolon with the use of a semiconductor laser «UPL PDT laser» («LEMT», Republic of Belarus, λ=661 nm) with exposure dose 100 J/cm² and power of laser radiation of 0.314 W and duration of photoirradiation of one focus was 15 min. (n=2). The area of photoirradiation included a section of healthy tissue, retreating from the edge of the tumor to 3-5 mm.

Assessment of tolerability and safety of the treatment was carried out for 30 days after the treatment on the basis of data on adverse events and reactions revealed in the course of treatment, their nature, frequency and severity. Given the specific characteristics of the disease and the treatment, the following side effects were assessed (CTCAE, Version 4.0, <http://www.meddrmsso.com>).

Clinical and cosmetic outcomes were evaluated after 1, 3 and 6 months. Clinical outcome was evaluated visually and morphologically by cytological or histopathological examination.

Performance criteria were as follows (according to WHO, 1979):

- complete regression: absence of all signs of the disease, 100% resorption of tumor foci in 1-3 months after PDT;
- partial regression: reduction of the total tumor size by 50% or more with subsequent stabilization, established after 1 month and confirmed 3 months after the PDT session;
- stabilization of the process: no increase in the size of the tumor nodes, the appearance of new nodes or other signs of disease progression within 3 months;
- progression of the process: an increase in the total size of the tumor node by 25% or more, or the development of new foci.

Estimating skin phototoxicity, it should be noted that patient, which observed the light regime for 3-4 days after the treatment session, avoiding direct sunlight, complications in the form of skin burns of various degrees and the development of hyperpigmentation was not observed.

The photodynamic effect in the form of increasing ischemic necrosis was observed by the end of the first week after treatment. Later, the patient conducted non-specific therapy, sanitation of the photoirradiation zone.

Completion of epithelial processes was fixed by week 5. The efficacy of the treatment was assessed after 1, 3 and 6 months according to the clinical examination, the vulvoscopy and the results of the cytological examination (Figure 1).



Fig. 1. Patient T., 54 years.
Clinical diagnosis: vulvar cancer in situ, $T_{is}N_0M_0$, stage 0:
a – clinical picture before PDT;
b – clinical «picture» 1 month after PDT (exposure dose – 100 J/cm^2)

At follow-up after 6 months, clinical and cytological signs of the disease were not identified.

3. RESULTS AND DISCUSSION

[Vulvar cancer is a serious medical and social problem, especially in young patients. Recognized treatment modalities include local excision, CO_2 laser ablation, CO_2 laser ablation in combination with surgical intervention, simple (cutaneous) vulvectomy with or without tissue graft transplantation and chemotherapy with application form of 5-fluorouracil (5% ointment) [1, 2, 3, 4].

One of the promising directions in the treatment of this pathology is photodynamic therapy. The main advantages of photodynamic therapy in comparison with traditional methods of treatment are:

1. minimal toxicity to the surrounding normal tissues, due to the selective accumulation of the photosensitizer in the tumor;
2. minimal risk of developing severe pain syndrome;
3. minor systemic effects;
4. lack of mechanisms of primary and acquired resistance;
5. the possibility of an outpatient procedure;
6. possibility of combination with other methods of treatment;
7. absence of limiting cumulative doses of photosensitizer and light exposure, ~~the possibility of repeated repetition of the procedure;~~
8. ease of use for the multiple nature of the lesion;
9. good cosmetic results;
10. the possibility of implementing organ-preserving methods of treatment.

In recent years, a number of authors' groups have presented the results of studies demonstrating the high antitumor efficacy of photodynamic therapy in the treatment of vulvar cancer [8, 9].

Professor Kaplan M.A. and colleagues reported a high incidence of complete regressions (45%, in 9 of 20 patients) achieved with photodynamic therapy (exposure dose 300 J/cm^2) with various photosensitizers (photogem, photosens and photolon) in 20 patients with morphologically verified vulvar carcinomas stage I (n=3), stage II (n=15), stage III (n=1) and stage IV (n=1). ~~With the relapse of the disease photodynamic therapy allowed to achieve clinical improvement in the form of a decrease in tumor volume by 30-50%, removal of edema of underlying tissues and reduction of pain syndrome [7].~~

In a study conducted under the guidance of Professor Filonenko E.V., the authors reported that the use of photodynamic therapy with intravenous injection of photolon at a dose of 1 mg/kg and application of 20% ointment of the preparation based on

5-aminolevulinic acid («Alasens») and subsequent photoirradiation in exposure doses of 100-350 J/cm² led to the development of a positive therapeutic effect at 3 months after treatment in patients suffering from vulvar croury (n=13), intraepithelial neoplasias of grade I-III (n=8) and squamous vulvar carcinomas (n=21). Complete clinical remission after 1 year after the treatment session was achieved in 40 (95.2%) patients. Side effects were pain syndrome after photodynamic therapy, which was stopped by the use of non-steroidal anti-inflammatory drugs [8].

4. CONCLUSION

[The results of the studies indicate good tolerability and antitumor efficacy of the method in the treatment of patients with vulvar carcinomas (stage 0/I; T_{is}/T₁), which in the long term can make photodynamic therapy one of the methods of choosing the treatment of this serious pathology].

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

Ethical committee approval has been taken.

REFERENCES

1. Alkatout I, Schubert M, Garbrecht N. et al. Vulvar cancer: epidemiology, clinical presentation, and management options. *Int J Womens Health*. 2015; 7: 305–13.
2. Woelber L, Kock L, Gieseck F. et al. Clinical management of primary vulvar cancer. *Eur J Cancer*. 2011; 47: 2315–21.
3. Corgevskaya EV, Kravetz OA, Kuznetsov VV, et al. Clinical recommendations of the association of Russian oncologists for the diagnosis and treatment of patients with vulvar cancer in situ, Moscow, 2014. Accessed 18 April 2017. Available: <http://oncology-association.ru/docs/recomend/may2015/06vz-rek.pdf>.
4. Dennis EJ. Photodynamic therapy for cancer. *Nature Rev (Cancer)*. 2003; 3: 380–87.
5. Castano AP, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. *Nature Rev (Cancer)*. 2006; 6: 535–45.
6. Tzerkovsky DA, Istomin YuP, Artemieva TP. et al. Sono-photodynamic therapy with photolon for recurrence glioblastoma grade IV: case report and review of experimental studies. *J Analyt Oncol*. 2016; 5: 62–6.
7. Krikunova LI, Mkrtchan LS, Kaplan MA. et al. The possibilities of photodynamic therapy of vulvar cancer. *Radiatsia and risk*. 2015; 24(2): 107–15 (in Russian).
8. Filonenko EV, Chulkova OV, Serova LG. The possibilities of photodynamic therapy in the treatment of dystrophic diseases, intraepithelial neoplasia and vulvar cancer. *Rus. Biother. J*. 2016; 15(1): 110–11 (in Russian).

DEFINITIONS, ACRONYMS, ABBREVIATIONS

Here is the Definitions section. This is an optional section.

Term: Definition for the term

APPENDIX