DOI: https://doi.org/10.17816/uroved90554
Review

Photodynamic methods of treatment of non-muscle-invasive bladder cancer

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The review article is devoted to the application of photodynamic therapy for non-muscle-invasive bladder cancer. The data on the mechanism and pathogenetic bases of the application of this treatment method, the method of its implementation, the advantages and disadvantages of the photosensitizers and the results of clinical studies are presented. It has been shown that intraoperative photodynamic therapy significantly reduces the rate of recurrence of bladder cancer after transurethral resection, including patients with carcinoma in situ and multifocal growth of urothelial tumors.

Keywords: bladder cancer; photosensitizer; photodynamic therapy; theranostics.

To cite this article:
Kasymov BG, Shanazarov NA, Muratov TM, Daniyarova GD, Zhumakayev AM, Kyzlasov PS, Kazhera AA, Slesarevskaya MN, Kuzmin IV, Al-Shukri SKh. Photodynamic methods of treatment of non-muscle-invasive bladder cancer. *Urology reports (St. Petersburg)*. 2021;11(4):355-363. DOI: https://doi.org/10.17816/uroved90554

Received: 15.11.2021 **Accepted:** 16.12.2021 **Published:** 29.12.2021

ECO•VECTOR

DOI: https://doi.org/10.17816/uroved90554
Обзорная статья

Фотодинамические методы лечения немышечно-инвазивного рака мочевого пузыря

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Обзорная статья посвящена применению фотодинамической терапии немышечно-инвазивного рака мочевого пузыря. Приведены данные о механизме и патогенетических основах применения данного метода лечения, методике его проведения, преимуществах и недостатках используемых фотосенсибилизаторов, представлены результаты клинических исследований. Показано, что интраоперационное проведение фотодинамической терапии существенно снижает частоту рецидивирования рака мочевого пузыря после трансуретральной резекции простаты, в том числе у пациентов с *carcinoma in situ* и при мультифокальном росте уротелиальных опухолей.

Ключевые слова: рак мочевого пузыря; фотосенсибилизатор; фотодинамическая терапия; тераностика.

Как цитировать:
Касымов Б.Г., Шаназаров Н.А., Муратов Т.М., Данияров Г.Д., Жумакаев А.М., Кызласов П.С., Кажера А.А., Слесаревская М.Н., Кузьмин И.В., Аль-Шукри С.Х. Фотодинамические методы лечения немышечно-инвазивного рака мочевого пузыря // Урологические ведомости. 2021. Т. 11. № 4. С. 355–363. DOI: https://doi.org/10.17816/uroved90554

Рукопись получена: 15.11.2021 **Рукопись одобрена:** 16.12.2021 **Опубликована:** 29.12.2021

ЭКО•ВЕКТОР

Bladder cancer (BC) is the most common malignant tumor of the urinary tract, which tends to recur and progress. Among all oncological diseases, BC ranks seventh in men and seventeenth in women [1]. The incidence of BC and mortality from it in men exceed those in women by 4.1 and 3.5 times, respectively [2]. When localized within the mucosal [stage Ta, *carcinoma in situ* (CIS)] or submucosal layers (stage T 1), BC is referred to as non-muscle-invasive (NMIBC). Upon diagnosis, NMIBC is detected in approximately 75% of patients [3]. According to the current clinical guidelines, the treatment of NMIBC should be started with transurethral resection (TUR) of the bladder tumor, and radical cystectomy is performed only in cases of total bladder damage [4]. After TUR, further treatment approach depends on the risk of recurrence and tumor progression. Moreover, regardless of the risk group, a single intravesical administration of a chemotherapy drug within 6 hours after TUR is indicated to all patients [5]. The low-risk group is further under case follow-up, and the intermediate and high-risk groups undergo adjuvant intravesical Calmette–Guerin bacillus (BCG) therapy or chemotherapy [5].

The incidence of tumor recurrence in patients with NMIBC after TUR is very high [6]. Even with adjuvant therapy, the probability of BC recurrence within 2 years reaches 60%, and the disease progresses to invasive forms in 25% of the cases [7]. In addition to the medical aspects associated with the insufficient treatment efficiency, the economic aspect is also relevant. Given the high recurrence rate, patients with BC require expensive studies, including invasive ones, with subsequent repeated surgical interventions. The total cost of treating a patient with BC during the lifetime is considered the highest among treatments of other types of cancer [8, 9].

The high incidence, high risk of recurrence, and tumor progression determine the relevance of increasing the efficiency of treatment for NMIBC. One of the options for research in this field is the study of possibilities of photodynamic therapy (PDT). The history of PDT goes back over a century. The term "photodynamic reaction" was first used in early 1900 by Professor Hermann von Tappeiner, who was the director of the Munich Pharmacological Institute. This was preceded by his discovery, together with his graduate student Oscar Raab, of the oxygen-dependent toxic effect of the fluorescent dye acridine orange on microorganisms, and the severity of this effect relied on the intensity of illumination. In 1903, von Tappeiner, together with dermatologist Albert Jesionek, proposed the use of photodynamics to treat skin diseases, including tumors [10]. This time can be considered the foundation of a new direction in medicine, now known as PDT. However, several decades later, this treatment method was not actively used, and the interest in it was only renewed in the second half of the XX century. Since then, active analysis of the possibilities of PDT in various fields of clinical medicine has started, studies of the fundamental principles of its therapeutic effect have been conducted, treatment methods have been developed, and new photosensitizers (PS) have been synthesized [11]. By the 1980s, PDT was already rightfully regarded as an effective method of treating various diseases, including cancer.

The clinical use of PDT is based on the interaction of three main elements, namely, oxygen, PS, and light radiation. PS can selectively accumulate in tumor tissues. When exposed to light energy of a wavelength corresponding to the maximum absorption of PS, it is activated, and photochemical reactions develop in the irradiated tumor, leading to damage to cancer cells. Moreover, neighboring healthy cells remain intact. The main mechanisms of the antitumor effect of PDT include a direct effect on tumor cells, disruption of the blood supply to tumors due to damage to the vascular endothelium, and activation of a nonspecific immune response [12].

Many aspects of PDT use in clinical practice remain unclear. Furthermore, the mechanism of the therapeutic action of PDT is quite complex, and it is impossible to distinguish any one single factor responsible for the death of tumor cells. The studies have helped establish that the absorption of light quanta by PS molecules in the presence of oxygen played the key role in the implementation of the photodynamic effect, which leads to two types of photochemical reactions, namely, the transformation of nontoxic triplet oxygen into singlet oxygen (type 1 reaction) and the formation of numerous active oxygen-containing radicals (type 2 reaction). The singlet form of oxygen in tumor destruction and the blood vessels feeding it gained major significance [13]. The lifespan of singlet oxygen in biological systems is short and does not exceed 0.04 ms, and the radius of cytotoxic action is approximately 20 nm [12]. Despite this, even a small amount of singlet oxygen triggers a cascade of biochemical and molecular reactions that have cytotoxic effects on tumor cells. Tumor cells die through three main mechanisms, namely, apoptosis, necrosis, and autophagy, and these processes can be activated separately or simultaneously [14].

The cytotoxic effect on tumor cells during PDT is determined by several parameters, and the main parameters include the type of PS used, extracellular or intracellular PS accumulation, PS dose, radiation power, and time interval between drug administration and exposure to light [15]. The main cellular targets for PS accumulation are the mitochondria, Golgi apparatus, endoplasmic reticulum, lysosomes, and cell membranes [15]. The method of penetration into the cell and intracellular targets are determined by the PS lipophilicity [16]. If the mitochondria become the sites of PS application, they are more likely to induce cell apoptosis, whereas those PS

that target the plasma membrane will primarily promote its necrosis [17]. In addition to the PS type, the nature of tumor cell death (apoptosis or necrosis) relies on the PS concentration and radiation dose. High doses of light energy lead to the development of necrosis, and in the case of PDT with low doses of light energy, the apoptosis mechanism is triggered [18].

In the treatment of patients with cancer, PDT is used as an independent method or in combination with surgical, radiation, or drug effects on the tumor [19]. In patients with NMIBC, PDT is currently recommended as the second line of antitumor therapy if previous treatment, including BCG prescription, was ineffective [5, 20].

The possibility of using PDT in BC was first reported by Kelly and Snell in 1976, and hematoporphyrin was used as a PS [21]. In 1983, Hisazumi et al. [22] used PDT with hematoporphyrin derivatives and an argon laser for the treatment of nine patients with 46 superficial Ta-T1 urinary bladder tumors. They noted the dependence of the clinical effect on the tumor size and radiation dose. Thus, in bladder tumors with a diameter of ⩽1 cm, exposure to laser radiation with an energy density of 100–250 J/cm^2 resulted in complete regression of the neoplasm in 5 of 6 patients. For tumors >2 cm in diameter, they recommended using the PDT parameters of light energy dose of 300 mW/cm^2, exposure time of 5–10 min or longer, and total light dose energy intensity of 100 J/cm^2 or higher. Moreover, complete destruction of the tumor was not noted in any case, if its size exceeded 2 cm [22].

In 1995, Uchibayashi et al. [23] published the results of PDT using hematoporphyrin in 34 patients with refractory CIS of the bladder. After 3 months, 25 (73.5%) patients noted complete tumor regression. Within 2 years, BC recurrence was detected in 14 (77.8%) of the 18 patients under follow-up. The authors noted a characteristic feature of these recurrent neoplasms, that is, most of them became superficial and low grade; subsequently, TUR was successfully performed in these patients [23].

With the accumulation of data on PDT using hematoporphyrin derivatives, evidence began to appear on the tolerability of this treatment, which was not always satisfactory. Phototoxicity reactions and bladder fibrosis as a result of its total irradiation were recorded relatively often, which limited significantly the widespread use of PDT [24]. This circumstance indicated the need to develop a safer PDT technique for the treatment of BC.

In 1987, the results of the use of 5-aminolevulinic acid (5-ALA) as a PS for photodynamic diagnostics and PDT in malignant neoplasms were first published [25]. The advent of 5-ALA gave an additional impetus to the introduction of PDT into clinical practice for the treatment of BC. 5-ALA is not a PS but is an inducer of the synthesis of endogenous PS protoporphyrin IX (PP IX), which has a maximum absorption peak at a light wavelength of 630 nm. When 5-ALA is introduced into the human body, it is rapidly utilized in healthy cells, and in tumor cells, given the lack of the ferrochelatase enzyme, as well as iron deficiency, the intermediate product of heme-PP IX biosynthesis accumulates. This leads to a significant difference in the level of PP IX between tumor and healthy cells, reaching 10–15-fold [26]. The accumulation of PP IX in the tumor tissue of the bladder occurs within 1.5–2 h after intravesical administration of 5-ALA. In an *in vitro* and *in vivo* animal study, 5-ALA demonstrated strong antitumor activity in urothelial cancer, mainly by enhancing apoptosis in cancer cells. 5-ALA-PDT also causes the death of neovascular endothelial cells in the tumor tissue, whereas no effect was found on the endothelial cells of small vessels in normal tissues surrounding the tumor [27].

The positive results of using 5-ALA during PDT for BC were confirmed by numerous clinical studies [28–31]. Waidelich et al. [30] performed PDT on the entire surface of the bladder in 12 patients with recurrent pTa G1-3 and CIS BC with multifocal localizations of the tumor foci 2–4.5 h after intravesical administration of 5-ALA at a total energy dose of 100 J/cm^2. Immediately after irradiation, a histological examination of tissues was performed. Viable cancer cells were not found in biopsy specimens from flat foci with a suspected tumor in any case, whereas such cells were detected in biopsy specimens from papillary lesions. Control examinations were performed in 11 of 12 patients, with an average follow-up period of 18 months. BC was not detected in 3 of 7 patients with CIS and in 2 of 4 patients with papillary tumors. Treatment tolerability was satisfactory. None of the patients had systemic side effects and a decrease in urinary bladder capacity. The authors concluded that PDT using 5-ALA is effective and safe in the treatment of urinary bladder malignant neoplasms [30].

The results of a Russian multicenter clinical trial confirmed the efficiency of TUR of a bladder tumor in combination with intraoperative PDT [31]. In that study, 50 mL of 3% Alasens® solution containing 5-ALA was injected into the bladder of 45 patients with NMIBC 1.5 hours before surgery. A PDT session was performed once immediately after the TUR using combined local irradiation of the excised tumor bed and diffuse irradiation of the entire bladder mucosa; the energy density of local irradiation was 100 J/cm^2, and the energy density of diffuse irradiation was 20 J/cm^2. The treatment was tolerated well, and no complications were recorded. Within 12 months of follow-up, 35 (78%) patients treated using this technique had no recurrences of BC. Thus, intraoperative PDT using Alasens reduced the frequency of NMIBC recurrence by 22% within 1 year after TUR. The results led to the conclusion that the frequency of NMIBC recurrence after TUR in combination with PDT is as good as that in standard adjuvant therapy of bladder tumors [26].

DOI: https://doi.org/10.17816/uroved90554

Another PS for intravesical administration during PDT is hexylaminolevulinate (HAL). Compared with 5-ALA, HAL is more lipophilic and is rapidly and evenly absorbed by urothelial cells [21]. HAL is converted to 5-ALA directly in tumor cells. HAL leads to a higher concentration of PP IX in tumor cells compared with 5-ALA [32].

The main drawback of 5-ALA-based PS is their small depth of penetration during intravesical administration (2–3 mm); therefore, the scope of these drugs is limited by the use for photodynamic diagnostics, as well as PDT of superficial BC in a mono mode and PDT in an adjuvant mode after surgical treatment of BC with a high recurrence risk [33]. In this regard, second-generation PS based on chlorins e6 (Photoditazine®) and a combination of e6, p6, and purpurin 5 (Radachlorin®) were developed and introduced in clinical practice. They have low phototoxicity and maximum absorption of light energy at a wavelength of 662 nm, and the photodynamic effect develops in tissues at a depth of up to 22 mm [34]. A distinctive feature of these drugs is the intravenous route of administration.

The first results of PDT with Photoditazine demonstrated its high efficiency in the treatment of NMIBC [35, 36]. In 2015, the results of a study on PDT efficiency using Photoditazine in 75 patients with NMIBC, conducted at the Clinic of Urology, First Pavlov Saint Petersburg State Medical University, were published. All patients underwent TUR of the bladder tumor and intraoperative PDT. Photoditazine was drip-feed injected at a dose of 0.8 mg/kg of body weight 1.5 h before surgery. After the TUR of the bladder tumor, the resection zone and surrounding tissues were locally irradiated with a laser at a wavelength of 662 nm. The light energy dose was 300–600 J/cm^2, and the radiation power was 1–2 W. The duration of the PDT session relied on the tumor size and was calculated individually for each patient. In the postoperative period, none of the patients had any local or systemic complications of PDT. The patients were followed up for 36 months, during which BC recurrence was detected in 12% of the patients in the main group (TUR + PDT); in the comparison group (TUR only), it was noted in 34.4% of the patients [37].

Lee et al. [38] analyzed the results of PDT with FS (Radachlorin) in 34 patients (22 men and 12 women) with high-grade NMIBC, who were unresponsive to BCG therapy and refused cystectomy. Radachlorin (0.5–0.6 mg/kg) was administered intravenously 2–3 h before PDT. Laser radiation was performed with a wavelength of 662 nm, output power of 1.8 W, and light energy dose of 15 J/cm^2. The duration of PDT varied from 16 to 30 min depending on the irradiation area. In control studies, no BC had relapsed after 12 months in 90.9% of the patients, after 24 months in 64.4%, and after 30 months in 60.1%. None of the patients reported serious side effects of therapy. Based on the results, PDT with intravenous administration of Radachlorin PS was considered the method of choice for patients with NMIBC who are resistant to BCG therapy or have individual intolerance to the BCG vaccine.

Salnikova et al. [39] performed a comparative analysis of the efficiency of PDT and traditional treatment methods of NMIBC. The main group included patients who underwent TUR of the bladder with photodynamic diagnostics and adjuvant PDT. The latter was performed according to the following scheme. At 2 or 3 h before TUR, PS (chlorin e6) was administered intravenously at a dose of 1–1.5 mg/kg, and after the drug accumulation, TUR of detected tumors was performed. Then, photodynamic diagnostics and repeated TUR of sites suspicious for cancer were performed. Thereafter, PDT was performed using an emitter with an output power of 2 W, wavelength of 662 nm, and light energy of 200–300 J/cm^2. In patients who were treated according to this scheme, no BC relapses were registered in 78.2% of the cases during control examinations after 3 years and in 76% after 5 years. Data obtained were significantly better than that in patients who underwent TUR alone and in those who underwent intravesical chemotherapy after TUR [39].

At the Hospital of the Medical Center of the Department of Presidential Affairs of the Republic of Kazakhstan, patients with NMIBC were treated using PDT according to the following scheme. TUR of the bladder tumor was performed to all patients. Before surgery, PS was administered intravenously for 30 min; then, 2 h after drug administration, intravenous blood photomodification was performed using a Lakhta-Milon laser device with an output power of 0.1 W and exposure time of 30 min. At 3 or 4 h after PS injection, local tumor irradiation was performed at a dose of 100–600 J/cm^{2}and wavelength of 660–670 nm. At the control cystoscopy, performed 3 months after TUR, all cases showed complete regression of tumors without disease recurrence [40, 41].

At present, the use of PDT, included in the treatment of NMIBC, has proved its efficiency. The main advantages of PDT of BC include (1) profitability, (2) selectivity of influence, (3) good tolerability, (4) possibility of multiple repetitions, and (5) the possibility of combining photodynamic diagnostics and therapy [33]. Photodynamic theranostics appears to be extremely promising, as it enables reduction of the number of diagnostic errors, determines tumor boundaries, takes into account the multicentric growth of BC, and allows intraoperative PDT as an antirelapse treatment [42].

The use of PDT in the treatment of NMIBC has proved its high efficiency and safety in many years. Currently, studies are being conducted in many countries to increase PS selectivity given their binding to molecules with an affinity for tumor tissues and have cytotoxic properties. The introduction of new PDT technologies will further increase the efficiency of this promising treatment method.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article. They have read and approved the final version before its publication.

Conflict of interest. The authors declare no conflict of interest.

Funding. The study received no external funding.

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