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Photodynamic diagnostics of non-muscle-invasive bladder cancer

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The review is devoted to the application of photodynamic diagnosis of non-muscle invasive bladder cancer. The recent data on the mechanism of action of photosensitizers, the method of performing fluorescence cystoscopy are presented, and the results of clinical studies of the application of photodynamic diagnostics in practical medicine are presented. It has been shown that photodynamic diagnostics significantly increases the efficiency of detecting bladder cancer in comparison with standard cystoscopy. The application of this method is especially valuable in cases of carcinoma in situ and multifocal growth of urothelial tumors. Improvement in diagnostics makes it possible to increase the radicality of surgical treatment and to increase the duration of the relapse-free period.

Keywords: non-muscle invasive bladder cancer; fluorescence cystoscopy; photosensitizer; photodynamic diagnostics.

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Фотодинамическая диагностика немышечно-инвазивного рака мочевого пузыря

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Обзорная статья посвящена применению фотодинамической диагностики немышечно-инвазивного рака мочевого пузыря. Приведены современные данные о механизме действия фотосенсибилизаторов, методике выполнения флуоресцентной цистоскопии, представлены результаты клинических исследований применения фотодинамической диагностики в практической медицине. Показано, что фотодинамическая диагностика существенно увеличивает эффективность выявления рака мочевого пузыря по сравнению со стандартной цистоскопией. Особенно ценным представляется применение данного метода в случаях carcinoma *in situ* и мультифокальном росте уротелиальных опухолей. Улучшение диагностики позволяет повысить радикальность хирургического лечения и увеличить длительность безрецидивного периода.

Ключевые слова: немышечно-инвазивный рак мочевого пузыря; флуоресцентная цистоскопия; фотосенсибилизатор; фотодинамическая диагностика.

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Bladder cancer (BC) is one of the most frequently diagnosed neoplasms and the most common malignant tumor of the urinary tract, ranking seventh in the structure of oncopathology in men and seventeenth in women [1]. The Russian Federation reported a BC incidence of 77.1 cases per 100 thousand population per year [2]. Superficial or non-muscle-invasive BC (NMIBC) is found in approximately 75% of patients upon initial diagnostics, which corresponds to stages Ta, T1, and Tis, and are characterized by the absence of muscle tissue infiltration [3]. The BC incidence at the non-invasive stage is even higher in patients under 40 years old [4].

Bladder wall transurethral resection (TUR) is still the main method for NMIBC treatment [5]. Consequently, the recurrence frequency of the tumor process after TUR is very significant, as it reaches 50% within 12 months and 78% within 5 years, and 45% probability of BC progression after 5 years [6, 7]. The high incidence of NMIBC recurrence after primary TUR is associated with many factors, mainly the degree of tumor malignancy, multicentric bladder mucosa lesions, and presence of undetected foci of cancer *in situ*, as well as possible tumor cell implantation during TUR [8, 9].

Early tumor diagnostics play a decisive role in the timely and effective treatment of patients with BC. Urine cytological examination, ultrasound, and cystoscopy with a bladder wall biopsy are used for the primary detection of BC in routine clinical practice [10].

Cystoscopy played a leading role in bladder tumor detection for almost 150 years. In 1878, the first working cystoscope was presented by the German urologist, Maximilian Nitze and the Austrian manufacturer of medical instruments, Joseph Leiter [11]. The importance of the inventions of Nitze and Leiter is not overestimated, even taking into account the technical imperfection of their proposed cystoscope. The greatest challenge was the provision of adequate bladder illumination, as in the first cystoscopes, thus the tungsten wire. Later, with technological development, a radical improvement in the optical properties of cystoscopes was achieved, which provided a high degree of bladder wall visualization. Modern instruments, standard cystoscopy, or white light cystoscopy detected neoplasms larger than 3 mm. In this case, flat endothelial pathological changes in the mucous membrane (dysplasia, cancer *in situ*) and small tumors often remain unnoticed, causing false relapses in 30%–75% of patients with BC within the next (2–6 weeks) period after TUR [12–15]. In addition, standard white light cystoscopy often disables the performance of differential diagnostics between inflammatory and tumor changes, as well as accurately determine the boundaries of the neoplasm and depth of invasion [16–18]. Therefore, increased efficiency of standard cystoscopic examination concerning BC detection was recognized by the urological community as one of the most significant problems in oncourology. Numerous studies in this field led to the emergence of new technologies for BC optical imaging.

The technological solutions implemented are conditionally divided into three groups, namely macroscopic, microscopic, and molecular [18, 19]. Macroscopic methods include photodynamic diagnostics (PDD), narrow-band imaging, and IMAGE1 S contact endocytoscopy (Storz Professional Image Enhancement System). These diagnostic methods are essentially similar to standard white light cystoscopy but with significantly greater diagnostic efficiency [15]. Microscopic imaging methods such as confocal laser endomicroscopy and optical coherence tomography performed the real-time bladder mucosa examination with high resolution at the cellular and subcellular levels, similar to the histological one, which allows a kind of "optical biopsy" consideration. Molecular methods are based on a combination of optical imaging technologies with fluorescence labeling of cancer-specific molecular agents, such as antibodies [20].

The PDD principle is based on the selective accumulation of the photosensitizer by tumor cells and the detection of a red glow characteristic when the photosensitizer is excited with blue light [21]. The investigation of the PDD possibilities initiated by the studies of J.F. Kelly and M.E. Snell (1976), demonstrated an experiment on a resected bladder, revealing the presence of fluorescence in the cells of a transient bladder cell tumor. A bright red glow was registered in the foci of carcinoma *in situ* (Cis), dysplastic changes in the mucous membrane, and exophytic tumors 24 h after the intravenous administration of hematoporphyrin at 2 mg/kg, wherein undetected in the normal mucous membrane and avascular urinary bladder tumors [22]. In 1982, the first fluorescence cystoscopy was performed using a fluorescent bronchoscopy device [23]. In the 1990s, a study was started on the possibility of using 5-aminolevulinic acid (5-ALA) in bladder tumor PDD. This substance is one of the intermediate products

of heme synthesis as a photosensitizer precursor [24]. Excessive administration of 5-ALA in the body leads to the inhibition of the last stage of heme synthesis and accumulation of its precursor, the endogenous protoporphyrin IX (PP IX). PP IX is rapidly disposed of under the action of the enzyme ferrochelatase and is converted into heme in intact tissue. This enzyme deficiency in tumor cells leads to a temporary but significantly increased level of PP IX, leading to the emergence of high fluorescent contrast in the accumulation of PP IX between the tumor and normal tissue, which reach 10–15 times [25].

For bladder tumor PDD, photosensitizing agents are intravesically injected, and are absorbed by the urothelium and included in heme biosynthesis of cells, leading to the intracellular accumulation of photoactive porphyrins in abnormal cells [13, 15, 26–32]. Under the influence of blue light (380–480 nm), dysplastic cells emit characteristic red fluorescence, which is easily visualized against the blue background of intact urothelium [28]. This substance is produced in the form of hydrochloride (the agent Alasense) due to the 5-ALA active instability. Immediately before instillation, 1.5 g of Alasense is diluted in 50 ml of 1.4% sodium phosphate monohydrogen and injected into the preliminarily emptied bladder.

No consensus was made regarding the exposure duration of 5-ALA in the bladder before fluorescence cystoscopy. Thus, the study by S.Kh. Al-Shukri et al. [33] revealed the exposure time as 60 min, and an increased endogenous PP IX within 120 min due to 5-ALA diffusion into the tumor cells of the bladder even after bladder emptying. N.A. Lopatkin et al. [34] did not indicate clear time parameters of the 5-ALA solution duration in the bladder, thus the exposure time varied from 1.5 to 3 h, averaging 114.1 min; however, the authors allowed the exposure to reduce to 60–80 min.

The duration of fluorescence of PP IX in blue light ranges from 10 to 20 min [25, 33], then the luminescence intensity significantly decreases. This process is called photobleaching. Moreover, its speed is significantly higher in blue light compared to white light and is directly proportional to the viewing distance and light flux intensity.

The PDD efficiency of bladder tumors using 5-ALA as a photosensitizer was proven in the course of a large number of clinical studies [13, 15, 17, 28–32, 35, 36]. A systematic review by I. Kausch et al. [31] demonstrated PDD sensitivity for BC detection in a range from 76% to 97% compared to 46%–80% for standard cystoscopy. The PDD efficacy was also confirmed by the authors of two meta-analyses, one of which reviewed 8 studies with 900 participants [15] and the other reviewed 27 studies involving 2807 patients [32]. The general conclusion based on these study results revealed that PDD sensitivity in detecting BC is 20% higher than that of standard cystoscopy. Concurrently, two other studies revealed that higher rates of BC detection were not obtained in PDD compared with that of conventional cystoscopy [37, 38].

The European Association of Urology recommended PDD for Cis diagnostics in 2006, this technique increases the Cis detection by 23% [31, 32, 39]. Thus, the study by A.M. Kamat et al. [40] revealed that Cis was detected only by PDD in 13 of 41 (32%) patients.

In addition, an important field of PDD is the detection of BC with a high risk of recurrence. A systematic review and meta-analysis by G. Mowatt et al. [32] revealed a sensitivity of fluorescence cystoscopy of 89% compared to 56% for white light cystoscopy in high-risk tumors diagnosis. The sensitivity of fluorescence cystoscopy was almost similar to that of the standard cystoscopy (92% vs. 95%) in tumors with a low risk of recurrence [32]. The use of PDD is very effective in patients with multifocal urinary bladder tumors, which is considered as an indication of its implementation [17].

With the accumulation of experience in PDD, biochemical characteristics of 5-ALA, such as hydrophilicity at physiological pH and low lipid solubility, lead to its insufficient bioavailability and rapid disappearance of tissue fluorescence (photobleaching) during cystoscopy, which limits the use of 5-ALA in clinical practice [3].

These limitations were overcome with the use of another compound, hexylaminolevulinate (HAL), which is characterized by higher lipid solubility, as well as rapid and uniform urothelial cell absorption. Inside the urotheliocytes, HAL is converted to 5-ALA, which ensures PDD [28, 41].

The PDD efficiency with HAL was confirmed by many studies, especially in Cis detection. The sensitivity of this technique in detecting bladder tumors is 49%–100% [3, 15, 42]. The frequency of Cis detection by PDD with HAL was approximately 25%–30% higher compared to standard cystoscopy [15, 29, 30].

A systematic review by R. Chou et al. [43] analyzed the results of 14 randomized studies evaluating the PDD efficiency using 5-ALA (6 studies) and HAL (9 studies) compared with white light cystoscopy to diagnose primary or recurrent BC followed by TUR. A total of 2906 patients participated in these studies. Study result analyses revealed that fluorescence cystoscopy decreased the recurrence rate of BC compared to white light cystoscopy in the short term (up to 3 months) and long term (>12 months). Concurrently, no differences were found in BC progression and mortality rates. However, conducting additional studies with long-term follow-up to understand the effect mechanisms of the photosensitizer on BC progression is necessary to confirm these results [43].

A study by I.G. Rusakov et al. [44] performed fluorescence cystoscopy in 198 patients with malignant bladder lesions, namely primary (n = 67) and recurrent (n = 131) transient BC cells. The agent Alasense developed based on 5-ALA was used as a photosensitizer. A sterile 3% Alasense solution was prepared for intravesical administration, and PDD was performed 2–3 h after the photosensitizer instillation. The fluorescent contrast of BC foci relative to the normal mucous membrane, measured using local fluorescence spectroscopy, was maximal at λ of 408 nm, its value varied from 10 to 35 (on average, approximately 15). At λ of 532 nm, the fluorescent contrast varied from 2 to 20 (on average, approximately 6). The fluorescent contrast of foci of nonspecific fluorescence (inflammation, moderate dysplasia, and inverted papillomas) did not exceed 4 at λ of 408 nm and 2 at λ equal to 532 nm. The authors concluded that the local fluorescence spectroscopy was used to measure fluorescence spectra in visual fluorescence foci and quantitative assessment of urothelium fluorescence increased the informational value and PDD efficiency of bladder neoplasms.

A multicenter clinical study conducted in Russia studied the PDD efficacy of bladder tumors using the Hexasens (HAL) photosensitizer, with standard cystoscopy comparison [45]. A total of 124 patients underwent intravesical instillation of 50 ml of 0.2% Hexasens solution, with 1–2 h exposure. After the agent was removed from the bladder, all patients underwent standard cystoscopy and then fluorescence diagnostics. Local fluorescence spectroscopy revealed that within 1 h after intravesical administration of Hexasens solution, the fluorescence level of Hexasens-induced PP IX in the tumor exceeded the level of its fluorescence in the surrounding healthy mucosa by an average of 5.8 times. PDD increased the BC detection efficiency by 24.4% (from 75.6% to 100%), diagnostic accuracy by 15.2% (from 83.3% to 98.5%), and the negative predictive value by 33.5% (from 66.5% to 100%) compared with the results of standard cystoscopy. Fluorescence diagnostics revealed additional tumor foci, which were undetected in the white light, in 27.4% of patients. False-positive fluorescence of the bladder mucosa was recorded in 4.0% of patients, which was possibly due to inflammatory processes in the course of fluorescence diagnostics. No patients, who received an active dose of Hexasens, showed adverse reaction development or changes in general well-being and blood and urine test results [45].

A study conducted at the Department of Urology, Pavlov First Saint Petersburg State Medical University compared the diagnostic efficacy of fluorescence cystoscopy using the second generation photosensitizer Fotoditazin and standard cystoscopy to detect NMIBC [8]. For PDD, 5 mg of Fotoditazin dissolved in 20 ml of physiological solution was injected into the bladder. The agent exposure time in the bladder ranged from 60 to 90 min. Cystoscopy was then performed sequentially in white and blue light. According to the study results, the diagnostic sensitivity of standard cystoscopy in white light was 62.3% and that of PDD with Fotoditazin was 96.7% [8].

A comparative assessment of Fotoditazin and Alasense usage for PDD of BC was studied by S.I. Gorelov et al. [46]. The authors monitored 144 patients with BC, who are distributed into three groups. Alasense was intravesically injected in 20 patients of group 1 at a dose of 1.5 g as a photosensitizer, the photosensitizer Fotoditazin was intravenously administered at 0.7–1.4 mg per kg of body weight in 48 patients of group 2; Fotoditazin was intravesically injected in 76 patients of the group 3 at 10.0 mg. The exposure for all methods of agent administration was 1.5–2 h, after which PDD was performed. TUR was performed when tumors or fluorescent areas of the bladder mucosa were detected. According to study results, the authors concluded that Fotoditazin, along with Alasense, is used for fluorescence diagnostics of bladder tumors due to the comparable sensitivity and specificity in papillary and flat bladder lesion diagnosis, with the fluorescence of Fotoditazin as more intense. In addition, the use of Fotoditazin is possible both intravenously and

intravesically; however, the intravesical dosage is 5 times less than intravenous administration. The PDD results of bladder tumors after intravesical and intravenous administration of Fotoditazin did not significantly differ.

In a study by K.M. Gallaghera et al. [47], treatment results of 345 patients with initially diagnosed NMIBC were analyzed. Patients were distributed into two groups. Group 1 (n = 153) consists of patients who underwent white light tumor TUR and group 2 (n = 192) with patients who underwent TUR under fluorescence control. In the absence of contraindications, Mitomycin C instillations were performed on all patients within 24 h after TUR. The advantage of TUR with PDD was revealed in the result evaluation. Concurrently, the rate of relapse-free survival rate in the group of patients with PDD (n = 192) was 52.9 months and 42.4 months in patients who underwent white light TUR (n = 153). The frequency of relapse detection in the group using PDD was lower in 1 and 3 years of follow-up (21.5% and 38.9%, respectively), whereas these indicators were 39.0% and 53.3%, respectively, in the group using conventional cystoscopy. In addition, the authors revealed that the PDD advantages did not depend on the experience of the surgeon performing the procedure [47]. M.R. Lykke et al. [48] also demonstrated a 41% decreased incidence of BC recurrence in patients who underwent TUR with PDD. The increased TUR efficiency in patients with BC using PDD was confirmed by Russian studies [49].

To date, publications demonstrating the positive clinical and economic effects of PDD are reported. Despite the increased cost of the procedure associated with PDD implementation, significant cost savings are achieved by reducing the number of BC relapses in the long term [50]. P.U. Malmström et al. [51] analyzed the treatment results of 2032 patients with newly diagnosed BC and revealed that fluorescence cystoscopy with HAL during the primary TUR and all subsequent TUR within 1 year after the diagnosis establishment gave a reason to refuse 23 cystectomies and 180 TUR in these patients.

The PDD high sensitivity in detecting BC in comparison with standard cystoscopy is beyond doubt and is confirmed by numerous study results [32]. Moreover, the PDD specificity is slightly lower than that of white light cystoscopy (63% vs. 81%) [31], which is due to the occurrence of false-positive mucosal glow in limited areas, caused by several factors, in particular, inflammatory bladder wall processes, including after a recent TUR, as well as instillations of Bacillus Calmette–Guérin, especially in the first 3 months after these procedures [52, 53]. D. Zlatev et al. [54] assessed the frequency of false-positive results of PDD of BC in 10%–12% of cases and associated them with autofluorescence of endogenous tissue fluorophores and high ability of immune cells to accumulate a photosensitizing agent. Therefore, PDD is not recommended in patients receiving intravesical immunotherapy or chemotherapy within the previous 90 days [3].

Urothelium dysplasia, especially squamous cell metaplasia, is also one of the common causes of false-positive fluorescence. Therefore, a nonspecific red glow is almost always seen with these changes in the mucous membrane in the bladder neck and prostatic urethra region. In addition, false-positive fluorescence occurs when the cystoscope is positioned at an acute angle to the bladder wall. This phenomenon is called tangential glow [55]. A simple method for differential tangential and pathological fluorescence diagnostics is reported. The suspicious area of the mucous membrane should be raised with biopsy forceps, which will change the angle of illumination of this area with blue light. If the fluorescence region disappears, then this phenomenon is regarded as tangential fluorescence. If the red glow persists, despite the manipulations, this region should be regarded as pathological and TUR should be performed in it [22].

CONCLUSION

The PDD significantly increased the efficiency of detecting NMIBC compared to conventional cystoscopy. Accurate diagnostics increased the radicality of surgical treatment, which ultimately increases the duration of the relapse-free period. Currently, PDD is recommended by most national urological communities for BC diagnosis, especially in patients at high risk of BC recurrence, multifocal lesions, and Cis. Concurrently, several issues related to the application of this technology remain unclear; therefore, further studies are necessary to understand the mechanism of action of photosensitizers, develop new drugs and techniques that reduce the number of false-positive results, and increase the fluorescence cystoscopy specificity.

ADDITIONAL INFORMATION

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

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