IMPROVING THE EFFICIENCY OF BLADDER CANCER DIAGNOSTIC CYSTOSCOPY WITH 5-ALA HEXYL ESTER

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Abstract

This article presents the results of a clinical study that examined the diagnostic efficacy of fluorescent diagnostics (FD) of non-muscular-invasive bladder cancer using a photosensitizer of FD of malignant neoplasms – 5-aminolevulinic acid hexyl ester (5-ALA HE) compared with standard cystoscopy. The study involved 110 patients. The study began with intravesical administration of 50 ml of 0.2% solution of 5-ALA HE, the exposure time was 1 hour, after which the drug was removed from the organ. During the next hour, the mucous membranes were examined in two cystoscopy modes, followed by a standard transurethral resection of all urothelium sites with suspicion for tumor lesion based on white light and visible red fluorescence, and a control blind biopsy from the visually unchanged and non-fluorescent mucous tissue in each patient. The results of the study indicate the high effectiveness of the developed FD methodology with 5-ALA HE in detecting non-muscular-invasive bladder cancer during intravesical administration of the drug, due to selective accumulation of hexasens-induced PPIX in the tumor tissue compared with healthy mucosa. Compared with the results of standard cystoscopy, fluorescence diagnostics significantly increased diagnostic sensitivity by 24.4% (from 75.1% to 99.5%), diagnostic accuracy – by 15.8% (from 82.4% to 98.2%) and a negative predictive value – by 33.2% (from 65.8% to 99%) ($p \leq 0.05$). Additionally, a total of 37 (33.6%) patients was found to have 63 foci of fluorescence with a diameter of 2.5 to 3.0 mm. 59 of these were morphologically confirmed to contain cancer cells.

Key words: 5-aminolevulinic acid hexyl ester, bladder cancer, fluorescent diagnostics.

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ПОВЫШЕНИЕ ЭФФЕКТИВНОСТИ ДИАГНОСТИКИ РАКА МОЧЕВОГО ПУЗЫРЯ ПРИ ИСПОЛЬЗОВАНИИ ЦИСТОСКОПИИ С ГЕКСИЛОВЫМ ЭФИРОМ 5-АЛК

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Резюме

В работе отражены результаты клинического исследования, в котором изучена диагностическая эффективность флуоресцентной диагностики (ФД) немышечно-инвазивного рака мочевого пузыря с использованием препарата для ФД злокачественных новообразований – гексилового эфира 5-аминолевулиновой кислоты (ГЭ 5-АЛК) в сравнении со стандартной цистоскопией. В исследование участвовали 110 пациентов. Исследование начинали с внутрипузырного введения 50 мл 0,2%-го раствора ГЭ 5-АЛК, время экспозиции составило 1 ч, после чего препарат удаляли из органа. В течение последующего часа проводили осмотр слизистой в двух режимах цистоскопии. Затем проводили трансуретальную рецзекцию всех подозрительных участков уротелия на опухолевое поражение в белом свете и из зон визуальной красной флуоресценции, а также у каждого пациента осуществляли контрольную «слепую» биопсию из визуально неизмененной и нефлуоресцирующей слизистой. Результаты исследования свидетельствуют о

высокой эффективности разработанной методики. Флуоресцентная диагностика по сравнению с результатами стандартной цистоскопии достоверно повысила чувствительность диагностики на 24,4% (с 75,1% до 99,5%), точность диагностики – на 15,8% (с 82,4% до 98,2%) и отрицательную прогностическую ценность – на 33,2% (с 65,8% до 99%) ($p \leq 0,05$). Дополнительно, в общей сложности у 37 (33,6%) больных, обнаружены 63 очага флуоресценции диаметром от 2,5 до 3,0 мм, на неизмененных в белом свете участках слизистой оболочки, в 59 из которых морфологически подтвержден рак мочевого пузыря.

Ключевые слова: гексиловый эфир 5-аминолевулиновой кислоты, рак мочевого пузыря, флуоресцентная диагностика.

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Introduction

The number of newly diagnosed cases of malignant neoplasms in the world is growing steadily, and bladder cancer (BC) is no exception. In the general structure of cancer incidence, this pathology has the 9th place [1]. In Russia, in 2017, bladder cancer accounted for 2.7% and had 70% in the total prevalence of all genitourinary system neoplasms. Bladder cancer is the second most prevalent urological disease and the third in the group in terms of lethality. Every year, over 13,000 patients in our country are registered with the diagnosis of bladder cancer diagnosed for the first time, and more than 6,000 patients with the disease die each year. Over the past ten years, an increase in incidence of 24.35% has been recorded, with an average annual increase of 2.15% [2].

An extremely important task is early detection of bladder tumors, the morphological structure of which in more than 90% of cases is represented by urothelial cancer. When bladder cancer is first diagnosed, 70–85% of cases are those of a non-muscle-invasive tumor (Ta, Tis, T1), which is diagnosed in the Russian Federation in no more than 30% of cases, which is significantly inferior to world best practices, where this figure reaches 80% [3, 4].

The problem of identifying early forms of bladder cancer is an urgent topic in modern oncourology, obviously related not only to untimely diagnosis of malignant tumors, but also to incorrect staging, where the error rate reaches 73% [5]. Bladder tumors with invasion no deeper than the mucosal/submucosal layer often remain unnoticed due to the impossibility of visualization of all the foci during standard cystoscopy in white light due to its resolution [6]. In some cases, this routine diagnostic method does not allow to determine the true boundaries of the lesion, to obtain sufficient information about the number of multifocal lesions, to assess the depth of the invasion, to visualize the foci of *carcinoma in situ* (CIS), and it also does not provide a sufficiently complete quantitative and prognostic characteristic of Ta and T1 tumors [7].

An inadequate assessment of tumor lesions in urothelium after transurethral resection (TUR) can lead to errors in the choice of treatment tactics, and also leads to a high risk of residual Cis, Ta, T1 foci, while in 81% of patients relapses are localized in the surgical area [8]. Moreover, standard cystoscopy does not make it possible to remove the tumor tissue completely, and its residual fragments often remain in the surgical margin of the resection, as it is diagnosed in 40–70% of secondary TUR [9]. These are not true recurrences, and they are more associated with many undetected tumor buds, fuzzy visualization of malignant changes in the resection margin, and false negative results of the biopsy taken randomly [10].

Thus, the limitations in the use of standard cystoscopy and its low information value in the diagnosis of intraepithelial tumor formations have led to an increased interest in studying the effectiveness of various diagnostic approaches capable of recognizing microscopic tumors, often outwardly not different from surrounding healthy tissues, and this was the beginning of the search for new modern techniques capable of improving the light marking of malignant neoplasms, among which the most promising is fluorescence diagnosis (FD). This method is based on the possibility of recognizing, with the use of special equipment, the pathological tissues by the characteristic fluorescence of exogenous or endogenous fluorochromes induced by light radiation, which makes it possible to clarify the boundaries of a tumor and detect foci that are not visible to the naked eye in white light [11].

The effectiveness of the method depends on the level of accumulation and localization of the dye in individual structures of the tumor focus and the surrounding tissue, which can be achieved by stimulating the body to produce endogenous photoactive compounds, porphyrins, in particular, endogenous photoactive protoporphyrin IX (PPIX) [12]. The induction of this biological substance is visualized by the high fluorescence contrast between the tumor and the surrounding tissue, which is important for identifying and clarifying the boundaries of the spread of the tumor, as the method simultane-

ously increases the radicalness of the surgical effect and reduces the damage to the tissues surrounding the tumor. Such a compound is 5-aminolevulinic acid (5-ALA), one of the intermediate products of synthesis of heme, the precursor of porphyrins, which is quickly utilized in healthy tissues, turning into heme under the action of ferrochelatase. Tumor tissue is found to be deficient in this enzyme, and with excessive administration of 5-ALA, a temporary but significant increase in the level of porphyrins occurs [13].

Continued research to improve the physicochemical properties of porphyrins and the diagnostic ability of PD has led to the development of a drug based on 5-ALA of the second generation, 5-ALA hexyl ester (HE 5-ALA), which is metabolized to 5-ALA in the body. Being more lipophilic compounds than 5-ALA, esters are better at penetrating biological membranes, so they accumulate in cells faster and to a greater extent, and become included in biosynthesis as PPIX precursors [14].

One of the promising directions for the use of HE 5-ALA as an agent for PD in oncourology is the diagnosis of early stage bladder cancer in the process called fluorescence cystoscopy with the use of blue light and various photosensitizers for marking tumors by intravesical administration [15, 16].

The purpose of the study was to increase the efficiency of the diagnosis of non-muscle-invasive bladder cancer with intravesical administration of 5-ALA hexyl ester.

Materials and methods

The study included 110 patients, more than half of whom had complaints were associated with a pre-cancer pathology of the genitourinary system, mainly those of disuria, discomfort in the bladder, as well as macro- and microhematuria. The study group was represented mainly by males, in a ratio of 3.7:1, aged over 60.

At the first stage, all patients underwent an outpatient screening examination in order to identify primary patients with non-muscle-invasive bladder cancer . Significant factors affecting the selection of patients were cystoscopy, echographic and, in some cases, X-ray studies which were used to evaluate the number and size of tumor foci and their localization.

Standard cystoscopy in white light mode and fluorescence mode was performed with the use of the instruments and equipment manufactured by Karl Storz (Germany), including a hard cystoscope equipped with a special filter with transmission characteristics corresponding to the maximum excitation in the blue range of the PPIX fluorescence spectrum (380-440 nm) which makes it possible to visualize pathological changes in urothelium against the background of surrounding healthy tissues. A hard resectoscope equipped with fluorescence optics, with an outer diameter of F26 was used for endo-surgical intervention on the bladder mucosa.

For fluorescence diagnostics, HE 5-ALA was used, which is an odorless, hygroscopic fine-crystalline white powder, readily soluble in water and water-salt solutions.

The study began with the intravesical administration of 50 ml of a 0.2% solution of HE 5-ALA, for the exposure of 1 hour, after which the solution was removed from the bladder. Over the next hour, a series of sequential and successive stages were carried out, which included standard and fluorescence cystoscopy and TUR of the tumor in PD conditions. During cystoscopy in the white light mode, attention was paid to the volume of the organ, changes in the state and color of the mucosa at the site where the search for pathological lesions was performed. The characteristics evaluated in the visualization of the tumor foci were their localization, macroscopic structure (the nature of the villi structure), size, growth pattern, quantity, condition of the surrounding mucous membrane, relation to the mouths of the ureters, the severity of the vascular pattern of the tumor itself and the submucosal layer.

The transition to fluorescence mode made it possible to identify the following types of sites: Type I: sites suspicious of cancer in white light and not fluorescent in blue light; Type II: sites suspicious of cancer in white light and fluorescent in blue light; Type III: additional foci that fluoresce in blue light with sizes from 2.5 to 3.0 mm in diameter and are not visible in ordinary light; Type IV: non-fluorescent normal white parts of the unchanged mucosa. After the completion of the mucosal examination in the two modes of cystoscopy, a standard TUR was performed in respect of all urothelium sites suspicious for tumor lesion in white light and the sites of visual red fluorescence, and in each patient a control "blind" biopsy was performed from a visually unchanged and non-fluorescent mucosa. Electroresection of the mucosa of the bladder was carried out within the mucosa or with the removal of the base of the pathological focus with muscle wall in order to determine the depth of the invasion in case the tumor nature of the changes is confirmed. After the completion of all stages of the study, a second blue-light inspection was performed to control the radical extent of TUR. Any fluorescent sites that were detected were resected. All the collected histological material was subjected to a routine study, the result of which was final in the diagnosis of intravesical pathology and made it possible to determine the nature of morphostructural changes in the bladder mucosa. The average number of foci studied in one patient was 3.2.

Focal formations of the bladder mucosa identified during cystoscopy in the two diagnostic modes were marked in accordance with the classification developed by P. A. Herzen Moscow Oncology Research Center: V (+): the tumor is determined visually when viewed in white light, V (-): when viewed in white light, the tumor is not determined; F (+): a focus of fluorescence, F (-): fluores-

cence is not determined; T (+): elements of a malignant neoplasm were detected, T (-): elements of a malignant neoplasm were not found. Depending on the results of standard and fluorescence cystoscopy and morphological data, a calculation was performed of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results.

Results

The total number of foci studied in the two modes of cystoscopy in all patients was 352: 179 (50.8%) with visually detectable pathology suspicious of the tumor process; 173 (49.2%) unchanged in the white light. Fluorescence was recorded in 241 (68.5%) of the foci; in the remaining 111 (31.5%), no fluorescence was observed. The bright fluorescence of HE 5-ALA-induced PPIX was visualized in 178 (99.4%) foci (V(+)F(+)) which in white light were found to have a cellular or rough mucosa with hypervascularization elevated relative to the surrounding tissues, and also those with single or multiple papillomatous growths. The majority of the villous formations had microscopic dimensions, less than 0.5 cm (79.6%), while the rest were up to 3.0 cm (12.5%) and over 5.0 cm (7.9%). Additionally, in 37 (33.6%) patients, 63 (36.4%) foci of fluorescence with a diameter of 2.5 mm to 3.0 mm were detected, unchanged in white light (V(-)F(+)), with the maximum number of such lesions found in one patient being 3. From the point of view of increasing the efficiency of bladder tumors diagnosis, the PD method is aimed at identifying these very areas that cannot be detected in white light but are highly likely to be tumors, and, therefore, are of considerable practical interest. Fluorescence was not determined in one focus with the clinical picture of hyperemia, which was highly suspicious of tumor changes (0.9%) (V(+)F(-)), and in all 110 (99.1%) areas of control biopsies (V(-)F(-)) (Table 1).

A histological examination of all urothelium biopsy specimens (n = 241) resected in the foci with bright fluorescence verifiedurothelial cancer (T+) in 236 (97.9%) of them, and non-specific inflammatory process in the remaining 5 (2.1%). Moreover, of 236 F(+)T(+) foci: there were 177 foci of V(+) and 59 foci of V(-); and among 5 foci F(+) T(-): there was 1 focus of V(+) and 4 foci of V(-).

In the study of 178 urothelium tissue samples represented in white light by foci of intense hyperemia highly suspicious of cancer and emitting bright fluorescence (V(+)F(+)) in blue light mode, tumor changes were detected in 177 (99.4%) of them (T(+)). In one (0.6%) biopsy sample collected in a cancer-suspected vascularization site, which in the blue light mode had a brightly fluorescent epithelium (V(+)F(+)), no tumor changes were found during histological examination, and a metaplastic process had place (T(-)).

A histological examination of 63 foci of additionally detected red fluorescence which in the white light mode looked like urothelium without pathological changes (V(-)F(+)) revealed transitional cancer (T(+)) in 59 (93.6%) of the foci. In all these cases, tumor growth was determined in multifocal buds not visible in the white light mode. In the remaining 4 (6.4%) foci of additional fluorescence (V(-)F(+)), which seemed unchanged in standard cystoscopy, inflammatory changes of a nonspecific nature were diagnosed: granular and glandular cystitis (T(-)).

In one focus (0.9%) of hypervascularization suspicious of a tumor process, but without fluorescence phenomena (V(+)F(-)), a nonspecific inflammatory process of glandular cystitis type was histologically diagnosed (T(-)) (Table 2). All data of histological examination of biopsy specimens performed according to the results of cystoscopic examination in the two imaging modes were statistically significant ($p \leq 0.05$). (Table 2.). It should be noted that in foci with visually unchanged mucosa, fluorescence was more intense with tumor lesions than in epithelium with a non-specific inflammatory process.

The morphological structure of tumors in all urothelium biopsy specimens was represented by transitional cell carcinoma of varying degrees of differentiation. Stages Ta-T1 and Tis were diagnosed in 156 (87.6%) and 21 (11.8%) foci of V(+)F(+), respectively, including low grade (G1): 51.1%, intermediate grade (G2): 38.6%; and high grade (G3): 10.3%. In 9 (15.3%) additionally identified foci with malignant changes in the surface epithelium (V(-)F(+)), Ta-T1 stages were established, and Tis was found in 50 (84.7%), with the degree of tumor differentiation being mainly G1 and G2. Almost the same percentage of CIS cases was found in tumors with exophytic growth and those almost undetectable in the white light mode. In the first case, the surface epithelium in the CIS localization zone was accompanied by the phenomena

Таблица 1
Результаты стандартной и флуоресцентной цистоскопии с ГЭ 5-АЛК при внутрипузырном введении

Table 1
Results of standard and fluorescent cystoscopy with 5-ALA HE with intravesical administration

Результаты стандартной цистоскопии и ФД Results of standard and fluorescent cystoscopy			
V(+)F(+)	V(–)F(+)	V(+)F(–)	V(–)F(–)
178 (73,8%)	63 (26,2%)	1 (0,9%)	110 (99,1%)
F(+) n=241		F(–) n=111	

«V(+)» – в белом свете определяется опухоль, «V(–)» – опухоль в белом свете не определяется, «F(+)» – участки флуоресцирующей ткани, «F(–)» – участки не флуоресцирующей ткани.

V(+) – tumor is detected in white light, V(–) – tumor is not detected in white light, F(+) – areas of fluorescent tissue, F(–) – areas of non-fluorescent tissue.

Таблица 2
Сопоставление результатов стандартной и флуоресцентной цистоскопии с данными гистологического исследования
Table 2
Comparison of standard and fluorescent cystoscopy results with histological examination data

Гистологическое исследование Histological examination	V(+)F(+)	V(+)F(–)	V(–)F(–)	V(–)F(+)
T(+) n=236	177 (75,0%)	–	–	59 (25,0%)
T(–) n=116	1 (0,9%)	1 (0,9%)	110 (94,8%)	4 (3,4%)
n= 352	n=178	n=1	n=110	n=63

«V(+)» – в белом свете определяется опухоль, «V(–)» – опухоль в белом свете не определяется; «F(+)» – участки флуоресцирующей ткани, «F(–)» – участки не флуоресцирующей ткани. «T(+)» данные морфологического исследования подтверждают наличие РМП; «T(–)» данные морфологического исследования не подтверждают наличие РМП.

V(+) – tumor is detected in white light, V(–) – tumor is not detected in white light, F(+) – areas of fluorescent tissue, F(–) – areas of non-fluorescent tissue, T(+) –the presence of bladder cancer is confirmed by morphology, T(–) – the presence of bladder cancer is not confirmed by morphology .

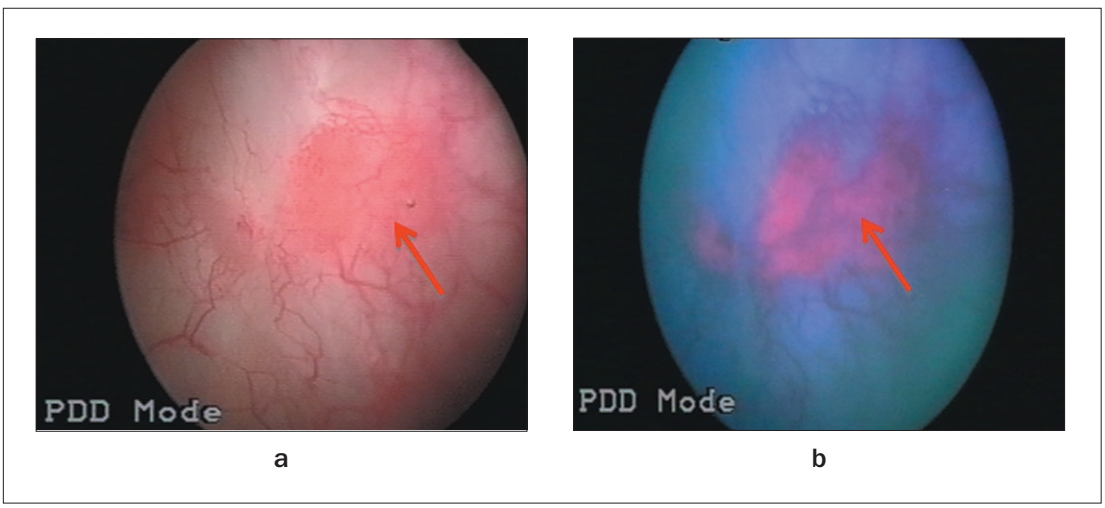


Рис. 1. Участок уротелия с картиной гиперемии подозрительного на рак характера *(a)*, флуоресцирующий ярким свечением *(b)*
Fig. 1. An area of urothelium with hyperemia with cancer-like characteristics *(a)*, with bright fluorescence *(b)*

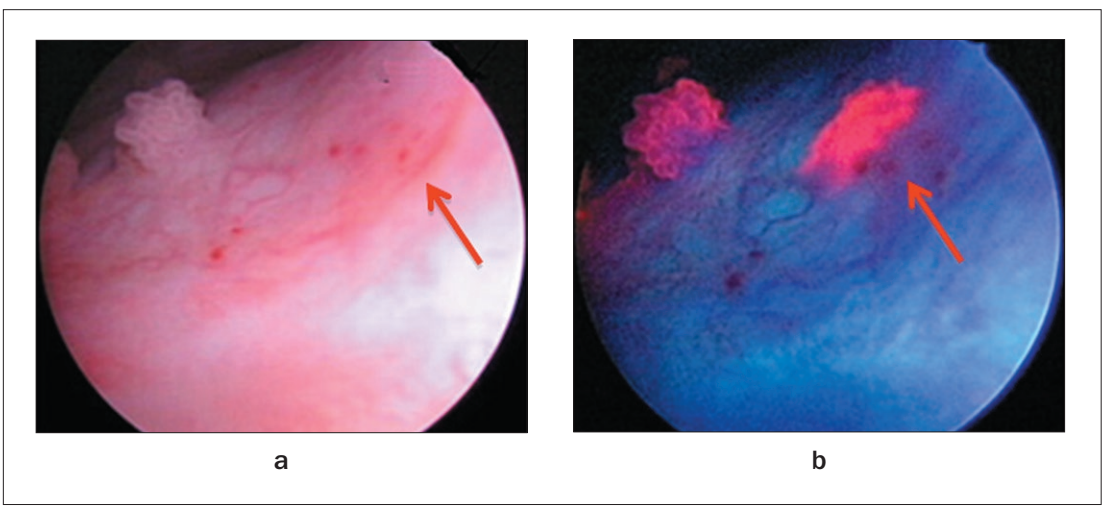


Рис. 2. Участок слизистой оболочки неизмененный в режиме белого света *(a)*, флуоресцирующий ярким свечением *(b)*
Fig. 2. An area of the mucous membrane almost unchanged in the white light mode *(a)*, with bright fluorescence *(b)*

Таблица 3
Оценка результатов цистоскопии в белом свете
Table 3
Evaluation of the results of cystoscopy in white light

Цистоскопия в белом свете Cystoscopy in white light	Всего Total	Морфологическое исследование Morphological examination		Оценка результатов Evaluation of results
		T(+)	T(–)	
V(+)	179	177 (97,6%)	2 (2,4%)	ИП 177; ЛП 2 TP 177; FP 2
V(–)	173	59 (34,2%)	114 (65,8%)	ЛО 59; ИО 114 FN 59; TN 114

«V(+)» – в белом свете определяется опухоль, «V(–)» – опухоль в белом свете не определяется. «T(+)» – морфологически подтверждена ткань опухоли, «T(–)» – морфологически подтверждена ткань мочевого пузыря.

ИП – истинноположительный. ИО – истинноотрицательный. ЛП – ложноположительный. ЛО – ложноотрицательный.

V(+) – tumor is detected in white light, V(–) – tumor is not detected in white light, T(+) –the presence of bladder cancer is confirmed by morphology, T(–) – the presence of bladder cancer is not confirmed by morphology .

TP – true positive. TN – true negative. FP – false positive. FN – false negative.

Таблица 4
Оценка результатов флуоресцентной цистоскопии
Table 4
Evaluation of the fluorescent cystoscopy results

Флуоресцентная цистоскопии Fluorescent cystoscopy	Всего Total	Морфологическое исследование Morphological examination		Оценка результатов Evaluation of results
		T(+)	T(–)	
F(+)	241	236 (97,9%)	5 (2,1%)	ИП 236; ЛП 5 TP 236; FP 5
F(–)	111	–	111 (100%)	ЛО 0; ИО 111 FN 0; TN 111

«F(+)» – участки флуоресцирующей ткани, «F(–)» – участки не флуоресцирующей ткани, «T(+)» – морфологически подтверждена ткань опухоли, «T(–)» – морфологически подтверждена ткань мочевого пузыря.

ИП – истинноположительный. ИО – истинноотрицательный. ЛП – ложноположительный. ЛО – ложноотрицательный.

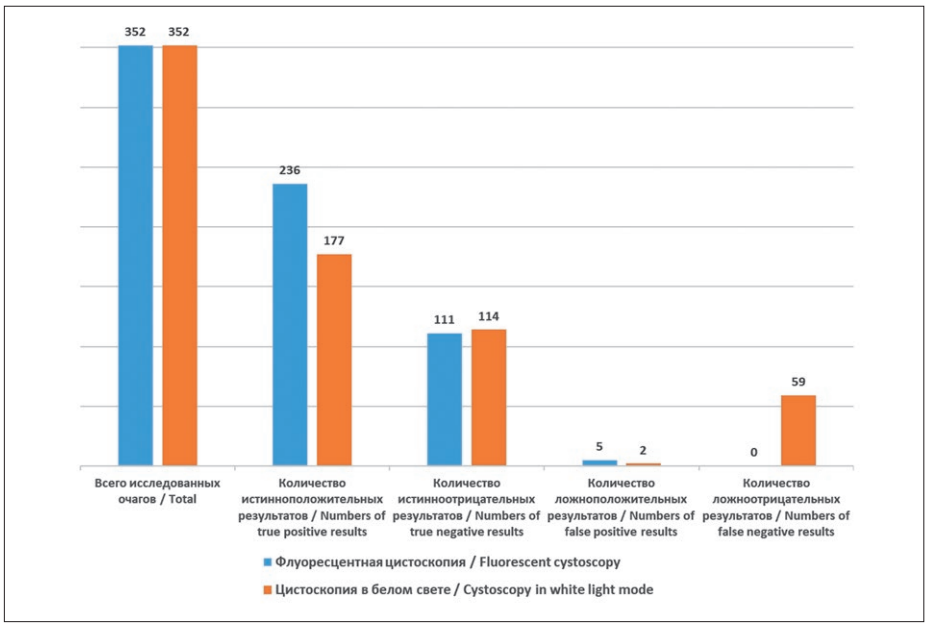
F(+) – areas of fluorescent tissue, F(–) – areas of non-fluorescent tissue, T(+) –the presence of bladder cancer is confirmed by morphology, T(–) – the presence of bladder cancer is not confirmed by morphology.

TP – true positive. TN – true negative. FP – false positive. FN – false negative.

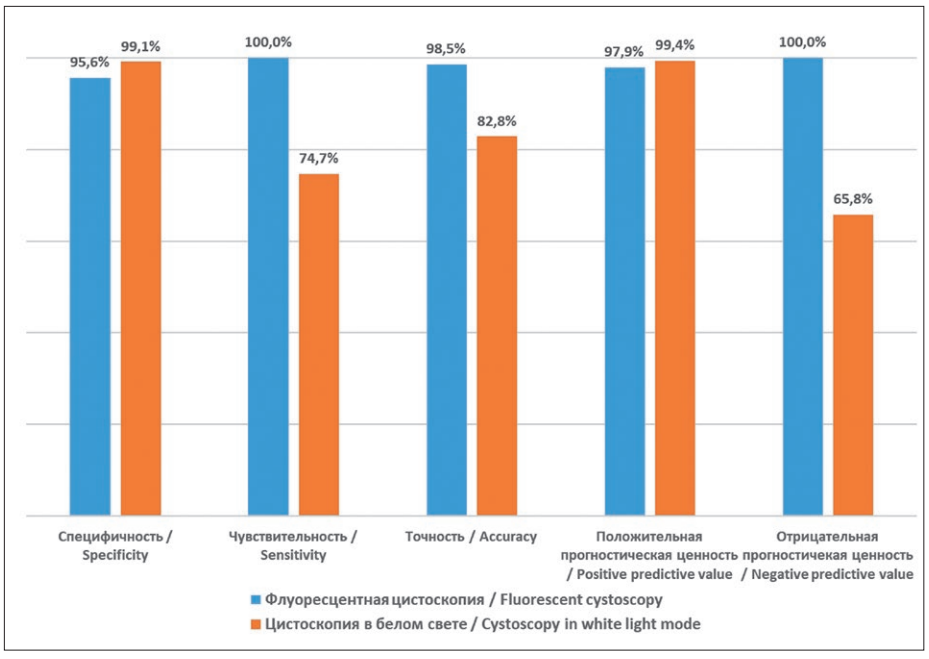
of hyperemia or inflammation, had a pronounced cellular or rough appearance (Fig. 1), in the second, the sites had virtually unchanged mucosa site (Fig. 2). Fluorescence with HE 5-ALA made it possible to detect intraepithelial malignant changes more than twice as often as with standard cystoscopy, since microscopic CIS can be skipped during cystoscopy or considered as an area of inflammation if a biopsy is not performed. In more than half of the cases (54.6%), these foci of tumor growth were isolated, in 32.6%, they were localized along the edge of papillary growths, and in a smaller percentage of cases, in their structure (12.8%).

With standard cystoscopy, 177 (97.6%) foci with visually determined tumor pathology were recognized as true positive. 2 foci (2.4%) were treated as false positive due to the absence of a malignant process in the test material, but the endoscopic pattern was highly suspicious of urothelial cancer. A false-negative result was found in 59 (34.1%) foci of urothelium unchanged in the white light, but the histological examination revealed non-muscle-invasive bladder cancer detected only by HE-ALK-induced PPIX fluorescence. True negative cases were reported in 4 (2.3%) tissue samples without visually detectable pathology, but with fluorescence phenomena caused by nonspecific inflammation. 110 (63.5%) control biopsies (V(-)F(-)) were also classified as true negative results, with tumor cells found in none of them (Table 3).

236 (97.9%) foci of bright red luminescence of HE 5-ALA-induced PPIX represented by transition-cell bladder cancer were classified as true positive (TP) results of fluorescence cystoscopy: 177 (75.0%) clinically determined and 59 (25%) additionally identified. In 5 (2.1%)



a



b

Рис. 3. Показатели диагностической эффективности флуоресцентной и стандартной цистоскопии *(a, b)*
Fig. 3. Indicators of diagnostic efficiency of fluorescent and standard cystoscopy *(a, b)*

fluorescence sites, the tumor process was not confirmed, which indicates a false-positive result: in 4 samples of resected urothelium, inflammatory changes of glandular and granular cystitis type were diagnosed, and metaplasia in 1 case. A truly negative result was established in 110 control studies (n = 110), in each of which there was no fluorescence and the tumor process was not detected. In one case (0.9%), a truly negative result was found at a site suspicious for cancer but without fluorescence phenomena, in which a nonspecific inflammatory process of glandular cystitis type was revealed. None of the studies found false negative results (Table 4).

The sensitivity of standard cystoscopy was 74.7%, its specificity: 99.1%. The positive predictive value was

99.4%, the negative predictive value was 65.8%. The accuracy value was 82.8%.

The sensitivity of fluorescence cystoscopy was 100%, and its specificity 95.6%. The positive predictive value corresponded to 97.9%, the negative predictive value was 100%, and accuracy rate was 98.5%. The results of the assessment of diagnostic parameters of cystoscopy in white light and in the fluorescence mode are shown in Fig. 3.

As can be seen from the data presented in Fig. 3b, PD significantly increased the sensitivity of diagnosis by 25.3% (from 74.7% to 100%), the accuracy of diagnosis by 15.7% (from 82.8% to 98.5%) and its negative predictive value by 34.2% (from 65.8% to 100%) ($p \leq 0.05$).

The sensitivity index seems to be a very important parameter at the stage of preoperative diagnosis, since it characterizes the possibility of identifying tumor foci that were not detected by standard cystoscopy and makes it possible to perform a more complete surgical removal of the tumor.

A greater number of false-positive results was obtained in PD (5 foci in 4 patients) than with standard cystoscopy (1 focus in 1 patient). These cases of false glow of urothelium were observed in the foci of inflammation, which led to a slight decrease in the specificity and positive prognostic value of PD (95.6% and 97.9%, respectively) in relation to the values of white light cystoscopy (99.1% and 99.4%, respectively) ($p \leq 0.05$).

A clinically significant difference in the diagnostic efficacy of fluorescence and standard cystoscopy was assumed to be a difference of more than 10%. Based on this value, we can conclude that the effectiveness of the PD method in terms of sensitivity, accuracy and negative prognostic value is significantly higher than the effectiveness of cystoscopy in white light. At the same time, the difference in specificity and positive prognostic value was significantly less than 10% (3.5% and 1.5%, respectively) and, therefore, cannot be considered clinically significant.

Conclusion

Thus, the results of the study indicate the high efficiency of the developed PD technique with the intravesical administration of HE 5-ALA in the detection of non-muscle-invasive bladder cancer due to the selective accumulation of HE 5-ALA induced PPIX in tumor tissue compared to healthy mucosa. The high contrast between the tumor and the surrounding tissues due to fluorescence revealed 59 additional tumor sites, which is 2.3 times higher than with standard cystoscopy. A significant increase in the diagnostic sensitivity from 74.7% (with standard cystoscopy) to 100% was achieved by detecting hidden foci of multifocal growth and determination of the true boundaries of the malignant process between the altered and unchanged epithelium, making them more clear and visible than with standard cystoscopy. The approach with the use of fluorescence during primary TUR determines the radical volume of treatment, which significantly reduces the likelihood of residual processes in the bladder mucosa, respectively reducing the risk of identification of a malignant process at a later stage, the development of relapses and disease progression.

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