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Comparative morphofunctional visualization of the manifestations of chronic bacterial and radiation bladder injuries

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Comparative morphofunctional and histological visualization of bladder wall lesions in 15 patients with chronic bacterial cystitis and in 15 patients with chronic radiation cystitis using positron emission tomography – computed tomography (PET/CT) was performed. The studies have revealed significant differences in the parameters of blood flow and tissue metabolism in patients with these forms of bladder lesions. In patients with chronic bacterial cystitis, an increase in the frequency of urination was accompanied by a decrease in the capacity of the bladder under conditions of a decrease in the velocity of arterial and venous blood flow in its wall as compared with the control. At the same time, at the cellular-molecular level in the bladder wall, no significant metabolic abnormalities, assessed by the SUV_{max} indicator, were revealed. Chronic radiation cystitis was characterized by a significant increase in the rate of systolic and diastolic blood flow in the bladder wall, its thickening and hypermetabolism of ^{18}F-FDG.

Keywords: PET/CT; imaging; chronic bacterial cystitis; chronic radiation cystitis.

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Сравнительная морфофункциональная визуализация проявлений хронических бактериальных и радиационных поражений мочевого пузыря

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Федеральное государственное бюджетное образовательное учреждение высшего образования «Тюменский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Тюмень

Проведена сравнительная морфофункциональная и гистологическая визуализация поражения стенки мочевого пузыря у 15 пациентов с хроническим бактериальным циститом и у 15 пациентов с хроническим радиационным циститом с использованием позитронно-эмиссионной томографии — компьютерной томографии (ПЭТ/КТ). Проведенные исследования выявили существенные различия параметров кровотока и тканевого метаболизма у пациентов с данными формами поражения мочевого пузыря. У пациентов с хроническим бактериальным циститом увеличение частоты мочеиспускания сопровождалось уменьшением емкости мочевого пузыря в условиях понижения скорости артериального и венозного кровотока в его стенке по сравнению с контролем. При этом на клеточно-молекулярном уровне в стенке мочевого пузыря существенных метаболических отклонений, оцениваемых по показателю SUV_{max}, не выявлено. Хронический радиационный цистит характеризовался достоверным увеличением скорости систолического и диастолического кровотока в стенке мочевого пузыря, ее утолщением и гиперметаболизмом ^{18}F-ФДГ

Ключевые слова: ПЭТ/КТ; визуализация; хронический бактериальный цистит; хронический радиационный цисти.

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INTRODUCTION

Chronic bacterial cystitis is primarily caused by a microbial pathogen that damages the urothelium and induces urothelial metaplasia. Further changes in the bladder wall are no longer caused by the bacterial pathogen; however, the changes are characterized by destructive and compensatory-adaptive reactions, alternation of dystrophic changes, and metaplasia with an increase in proliferative activity and focal alteration [1, 2]. A main mechanism of radiation to the bladder is damage to the endothelium of the capillaries and arterioles, with the occurrence of a chronic abacterial inflammatory process. Its combination with the direct effect of the ionizing factor on the entire depth of the urinary bladder tissue structures induces the development of a radiation pathological process [3–5]. Radiobiological studies revealed that it takes approximately 100 days to restore sublethally damaged cells of the urinary bladder; however, in some cases, in case of weakening of reparative processes and an abrupt slowdown in the regeneration of the affected structures, the pathological process terminates during incomplete secondary alteration and reparative restoration of damaged tissues [6–8]. The clinical manifestations of chronic bacterial and radiation-induced cystitis develop 3–6 months from contact with a bacterial pathogen or radiation damaging factor, not complicated by the bladder infection, and are accompanied by dysuria. The typical cystoscopic signs in both cases were mucosal hyperemia with edema of the trigone of the bladder and the ureteral orifices, which is often accompanied by a decline in urine evacuation through the upper urinary tract [9–11].

This study aimed to perform comparative morphofunctional and histological visualization of manifestations of chronic bacterial and chronic radiation damage to the urinary bladder.

MATERIALS AND METHODS

In this study, we performed a comparative morphofunctional and histological visualization of manifestations of bladder lesions between 15 patients (10 women and 6 men) with chronic bacterial cystitis (CBC) and 15 patients (9 women and 7 men) with chronic radiation cystitis (CRC). The median age of the patients examined was 45.5 years [36; 54], and the duration of clinical manifestations of the disease ranged from 3 to 6 months. The patients provided informed consent to participate in the study. Patient complaints and laboratory parameters of the urinary sediment study almost did not differ between the two groups. Bacteriological examination of urine in CBC revealed *Escherichia coli* in 11 (73.3%) patients, *Enterococcus* in 2 (13.3%) patients, *Klebsiella* in 1 (6.7%) patient, and *Proteus* in 1 (6.7%) patient with sensitivity to fluoroquinolones and nitrofurans. In patients with radiation cystitis, *E. coli* with a wide range of sensitivity was found in only 3 cases (20%); hence, in other cases, the urine was considered conditionally sterile.

The comparison group consisted of 8 women and 7 men (n = 15) without a nephro-urological history who underwent the current clinical examination and were considered healthy. At the diagnostic stage, all patients underwent uroflowmetry, bladder ultrasonography with Doppler imaging of the vessels, and cystoscopy with biopsy of the bladder wall in areas of the greatest visual changes (for comparison, the results of sectional bladder biopsy in five people without nephro-urological history were used). Combined positron emission tomography-computed tomography (PET/CT) of the whole body with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and native PET of the kidneys and urinary bladder were performed on a Siemens Biograph (Siemens, Germany) PET/CT apparatus in the radiological center of Tyumen regional oncology dispensary. Functional changes in the bladder wall were studied by the foci of changes in tissue tropism to energy-intensive molecules with ^{18}F-FDG. Segments of interest were analyzed automatically according to the level of isotope uptake (SUV_{max}, Standard Uptake Value) and evaluated in relative units. Isotopes were prepared at the Radiological Center on the Scanditronix compact cyclotron (Sweden).

Processing and systematization of the material obtained were performed using the Microsoft Excel spreadsheet software package and the Statistica v.10 software package. Methods of variation statistics were applied, and the data obtained were presented as $M \pm m$. The arithmetic mean, M; the error of the arithmetic mean, m; and the normalized deviation, t (Student's test) were determined. $p < 0.05$ was considered statistically different.

RESULTS

The comparative characteristics of the functional manifestations of bacterial and radiation lesions of the urinary bladder are presented in Fig. 1.

In CBC patients, according to uroflowmetry performed at the first urge to urinate, a decrease in the volume of micturition was noted with an increase in the duration of urination. In radiation injury to the detrusor, a decrease in the single volume of micturition at the first urge did not affect the duration of urinary bladder emptying. There were no gender differences in the revealed aspects of the urination process (Fig. 1, I).

Bladder ultrasonography with Doppler imaging of the vessels, performed in CBC patients during the first urge to urinate, showed a decrease in the velocity of arterial and venous blood flow in the vessels of the urinary bladder wall. In patients with radiation injuries of the bladder, a significant increase in the detrusor thickness

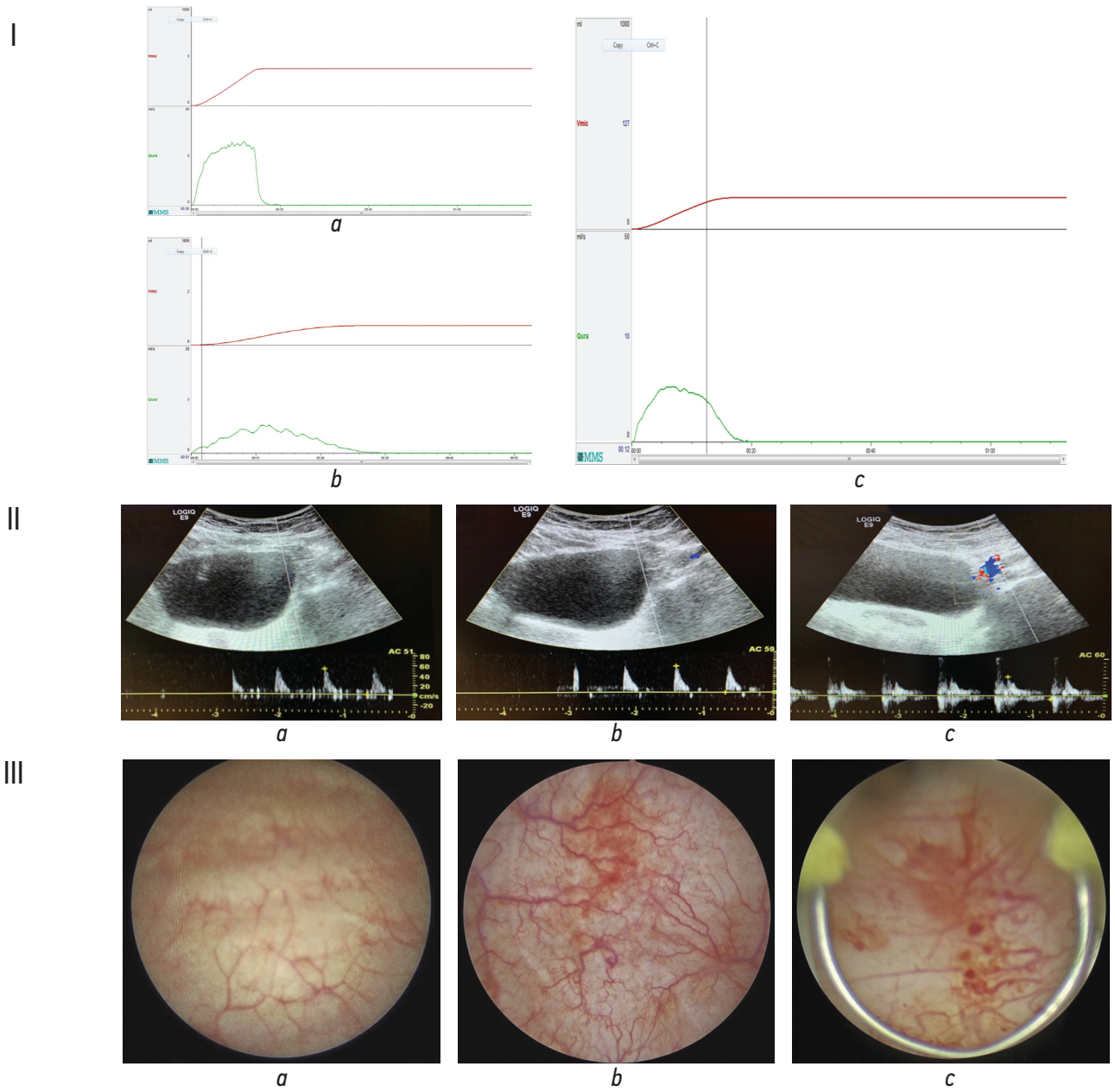

Fig. 1. Functional and morphological visualization of microbial-inflammatory and radiation damage to the bladder: I – uroflowmetry; II – ultrasonography of the bladder with Doppler ultrasonography; III – cystoscopy. *a* – control group; *b* – chronic bacterial cystitis; *c* – chronic radiation cystitis

Рис. 1. Функционально-морфологическая визуализация микробно-воспалительного и радиационного поражения мочевого пузыря: I — урофлоуметрия; II — ультрасонография мочевого пузыря с доплерографией; III — цистоскопия. *a* — контрольная группа; *b* — хронический бактериальный цистит; *c* — хронический радиационный цистит

and velocity of both arterial and venous blood flow was noted (Fig. 1, II).

The cystoscopic presentation in the absence of clinical and laboratory manifestations of chronic cystitis (e.g., with prophylactic catheterization of the ureters prior to extensive abdominal interventions) was characterized in our cases by a mild injection of the vessels of the bladder mucosa. With clinical manifestations of CBC, vascular injection and mucosal hyperemia were more noticeable and mainly covered the neck. CRC was characterized by polyfocal nature of manifestations such as telangiectasias with mucosal erosion in their projection (Fig. 1, III).

Thus, based on the study results, we suggested that in CBC, the pathological process involves mainly the surface structures of the bladder wall, and the filling and emptying phase of the urination cycle could be a consequence of detrusor ischemia accompanied by neurogenic regulation impairment. For CRC, the damage to deep structures with a compensatory increase in their blood supply and secondary local involvement of the mucous membrane segments, with the

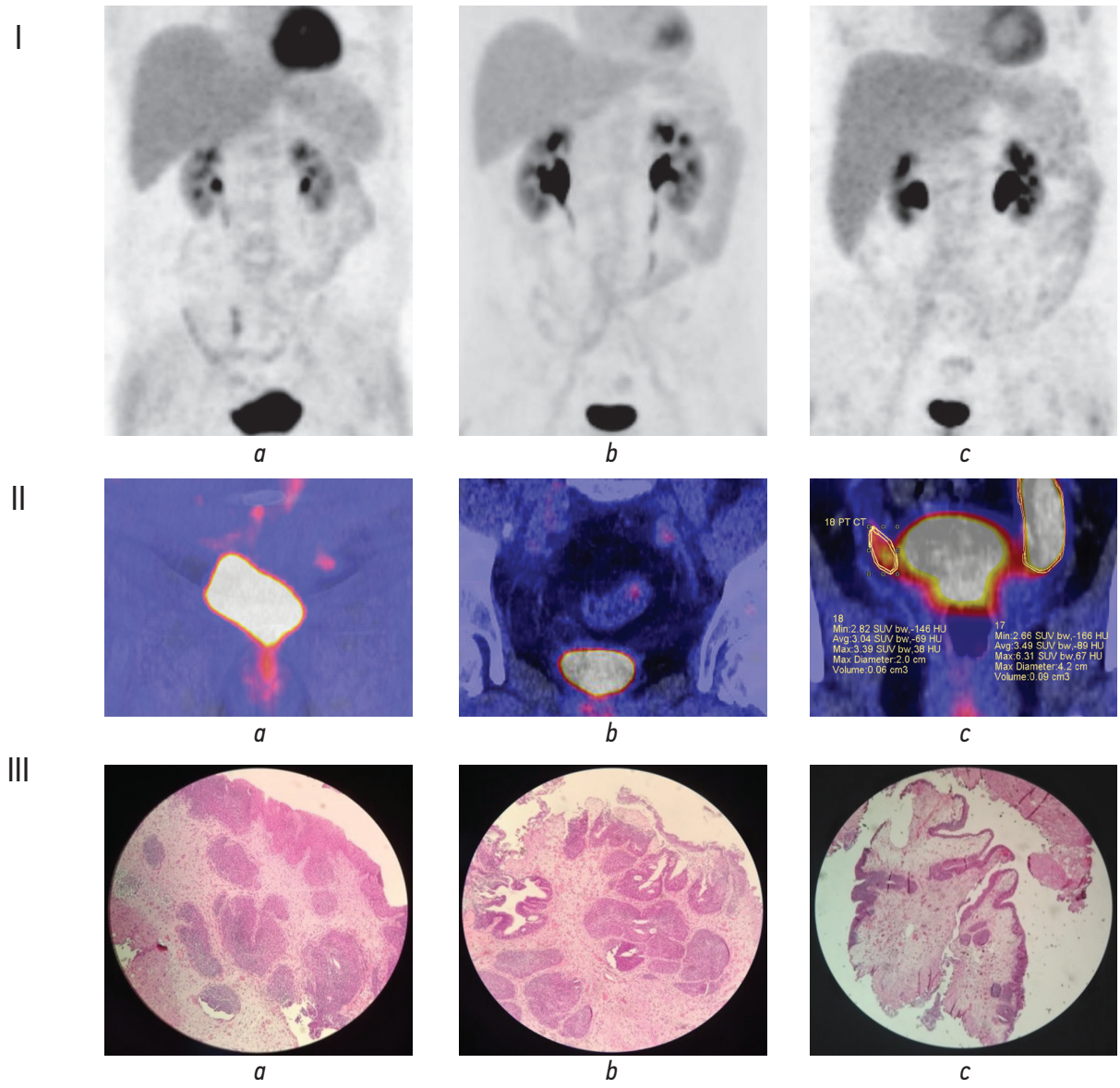

Fig. 2. Comparative molecular cell and histological imaging of chronic bacterial and chronic and radiation damage to the bladder: I – native positron emission tomography of the upper and lower urinary tract; II – combined positron emission tomography with computed tomography of the bladder; III – histological examination of the bladder wall (stain hematoxylin-eosin). *a* – control group; *b* – chronic bacterial cystitis; *c* – chronic radiation cystitis

Рис. 2. Сравнительная молекулярно-клеточная и гистологическая визуализация хронического бактериального и хронического и радиационного поражения мочевого пузыря: I — нативная позитронно-эмиссионная томография верхних и нижних мочевых путей; II — совмещенная позитронно-эмиссионная томография с компьютерной томографией мочевого пузыря; III — гистологическое исследование стенки мочевого пузыря (окраска гематоксилином и эозином). *a* — контрольная группа; *b* — хронический бактериальный цистит; *c* — хронический радиационный цистит

formation of sluggish granulating erosions, were more common.

The data obtained did not contradict the conventional ideas about the aspects of chronic bacterial and radiation lesions of the bladder; however, they required a more conclusive evidence based on contemporary high-tech PET/CT molecular cell imaging of the process under study and its comparison with the results of traditional histological examination. Figure 2 presents the results of PET/CT molecular cell imaging of the manifestations of chronic bacterial and radiation damage to the bladder and a comparison of the histological examination results.

Figure 2 (I) shows the variants of native PET of the upper and lower urinary tract without X-ray image intensifying, which represent the real-time visualization of the metabolism of energy-intensive glucose molecules at the molecular-cellular level of the urine formation and urine excretion processes. Normally, at the first urge to urinate, the renal parenchyma synchronously included labeled glucose into the structural formations, and the excess was removed by excretion from the upper urinary

Table. Clinical indicators and results of instrumental examination of patients with chronic bacterial cystitis and chronic radiation cystitis and persons of the control group, $M \pm m$

Таблица. Клинические показатели и результаты инструментального обследования больных хроническим бактериальным циститом и хроническим радиацинным циститом и представителей контрольной группы, $M \pm m$

Indicator	Control group (n = 15)	CBC (n = 15)	CRC (n = 15)
Frequency of urination, per day	7.1 ± 0.5	10.8 ± 0.7*	8.6 ± 0.5
Systolic blood flow velocity in the bladder wall, cm/s	9.2 ± 0.5	5.3 ± 0.5*	10.5 ± 0.3*
Diastolic blood flow velocity in the bladder wall, cm/s	3.4 ± 0.5	2.2 ± 0.3*	2.9 ± 0.2*
Resistance index	0.63 ± 0.05	0.68 ± 0.04*	0.72 ± 0.03*
Bladder wall volume (according to PET), cm^3	0.09 ± 0.2	0.15 ± 0.6	0.24 ± 0.4*
SUV_{max} (according to PET), relative units	5.03 ± 0.5	6.23 ± 0.5	10.13 ± 0.5*

*$p < 0.05$ differences with the value of the norm indicator are statistically significant. *Note*: CBC, chronic bacterial cystitis; CRC, chronic radiation cystitis; PET, positron emission tomography.

tract into the bladder (Fig. 2, *a*). In CBC, with a decrease in bladder capacity, a delay in the urine passage from the upper urinary tract was noted (*b*). In CRC patients, both a disorder of the urine passage from the upper urinary tract and a slowdown in glucose metabolism in the parenchyma of both kidneys were observed (*c*).

Figure 2 (II) presents a combined PET/CT scan of the bladder, demonstrating the metabolic activity of energy-intensive glucose molecules directly at various levels of its wall (*a*). In CBC, manifested by a decrease in the bladder capacity at the first urge to urinate, the activity of glucose metabolism in its wall did not change significantly (*b*), whereas in CRC patients, manifestations of pronounced hypermetabolism of ^{18}F-FDG were noted in cell formations involved in chronic pathological process (*c*).

Figure 2 (III) presents the results of a morphological study of the bladder tissue obtained by biopsy. Thus, in the bladder preparation of the control group representatives without a nephro-urological history, the wall was covered throughout with urothelium with intact layer stratification, with a normal structure of the umbrella cell layer and the basement membrane (*a*). In the bladder wall preparation of the patients manifesting CBC, the areas of the mucosa with diffuse metaplasia and papillary outgrowths partially covered with normal urothelium were detected. In its stroma, cutoff invaginates of hyperplastic urothelium without atypia were visualized (*b*). A sluggish diffuse lymphoplasmacytic infiltration of tissues with rare foci of glandular metaplasia (*c*) was noted in the bladder wall preparation with manifestations of CRC.

Table 1 shows the results of examination of the CBC and CRC patients and representatives of the control group.

CONCLUSIONS

Studies have revealed significant differences between blood flow and tissue metabolism in CBC and CRC patients. In CBC patients, an increase in the frequency of urination was accompanied by a decrease in bladder capacity under decrease in the velocity of arterial and venous blood flow in its wall compared with that in controls. Moreover, at the cellular-molecular level in the bladder wall, the SUV_{max} indicator revealed no significant metabolic abnormalities. CRC was characterized by a significant increase in the velocity of systolic and diastolic blood flow in the urinary bladder wall, its thickening, and hypermetabolism of ^{18}F-FDG.

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