

соматичною симптоматикою з урахуванням патогенних факторів та їх патоморфозу. Зроблено висновок, що доказове використання при лікуванні психічних розладів із соматичними симптомами з урахуванням патогенних факторів та їх патоморфозу передбачає переважне застосування прегабаліну як універсального стабілізатора балансу нейромедіатора в терапії як тривожних, так і інших психогенних розладів.

**Ключевые слова:** психогенные расстройства, тревожные расстройства, нейромедиаторы, прегабалин, соматический компонент, дифференциальная терапия

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соматическими симптомами с учетом патогенных факторов и их патоморфозов. Был сделан вывод о том, что доказательное использование в лечении психических расстройств с соматическими симптомами с учетом патогенных факторов и их патоморфозов предполагает преимущественное использование прегабалина в качестве универсального стабилизатора нейромедиаторного баланса в терапии как тревожных, так и других психогенных расстройств.

**Ключевые слова:** психогенные расстройства, тревожные расстройства, нейромедиаторы, прегабалин, соматический компонент, дифференциальная терапия.

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## DYNAMIC CHANGES IN THE CELLULAR COMPOSITION IN THE UROPSAMMUS OF ARTIFACTUAL BLADDER

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The purpose of the work was to evaluate the dynamic changes in the cellular composition of the artificial bladder uropsammus. The dynamics of structural changes in the urine sediment after surgery was revealed, which indicates that, in the presence of positive clinical results after the operation, the processes of restructuring the epithelial lining of the intestinal fragment transplanted instead of the bladder, aimed at performing other functions, are being completed. Based on the data obtained, it is possible to use a cytological study in the clinic to establish the dynamics of the process after surgical treatment, to determine the degree of epithelium exfoliation in the transplanted intestine, as well as to correct individual links of the adaptation process under the new conditions of the transplanted intestinal fragment functioning, which are fundamentally different.

**Key words:** artificial bladder, cell composition, adaptation.

*The work is a fragment of the research project "Phenomenology, pathogenesis, features of clinical course, topical diagnosing and treatment of dysfunctional pelvic pain syndromes and neurogenic disorders of urination", state registration No. O115U006656.*

The gold standard of treating the muscular invasive cancer of the bladder is the radical cystectomy with the orthotopic bladder formation [4, 6]. Many studies have been carried out on the safety and efficacy of using a fragment of the colon and small intestine, stomach, but the best transplant is considered to be a site of the terminal ileum: due to the smallest electrolyte disturbances and the ability of adaptive restructuring it is considered the optimal transplant [3].

Initially, the ileum mucosa contains many cells: Paneth cells, goblet, absorbent, enteroendocrine, stem, undifferentiated, and M-cells with known diverse functions [5]. The enterocyte microvilli are covered with a glycocalyx membrane, which contains various protective proteases, lysozyme, etc. [10]. The physical barrier is formed by the mucosal epithelial absorbent goblet cells and mucus secreted by the latter [1].

Functioning of the ileum site under new conditions, the influence of urinary components on the artificial bladder's mucous membrane, the possibility of adaptation and transformation of the neocyst epitheliocytes, early detection of atypical cells have determined our interest to the study of the urine sediment cytological features in dynamics. The data of the researchers are quite diverse: some scientists report the hypersecretion of sulfomycin, sialomycin, progressive microvilli atrophy, adenomatous hyperplasia and dysplasia of mucous cells in the artificial bladder [13, 14]. Cytological control of atypical cells is defined by many authors as a non-invasive way of early detecting the recurrence of urothelial carcinoma [7].

In the routine practice, study of urine sediment is an integral and important part of the general urine analysis. The main elements of organized urinary sediment are erythrocytes, leukocytes, epithelium, and cylinders; unorganized sediment includes crystalline and amorphous salts. Normally in the field of view of the microscope, single cells of the squamous (urethra) and transitional epithelium (bowel, ureter, bladder) are detected. The renal epithelium is normally absent.

**The purpose** of the work was to assess dynamic changes in the cellular composition of the artificial bladder's urine sediment (uropsammus).

**Materials and methods.** The study of the urinary sediment cellular composition was performed in 26 patients after radical cystectomy with orthotopic ileocystoplasty for muscular invasive bladder cancer

within the periods of 1; 3; 6; 12 months and 2 years. The urine sampled from the artificial bladder was centrifuged, the sediment was fixed on a slide.

Specimens, obtained as a result of the urine precipitation after fixation with 10% neutral formalin and dehydration in alcohols, were stained with hematoxylin and eosin. Light optical microscopy and photographing were performed using JNAMED2 microscope.

**Results of the study and their discussion.** One month after the surgery, the microscope's field of view is almost completely covered with large layers of quite differentiated epithelial tissue with inclusion of swollen goblet cells. Layers of epithelial tissue have a concentric structure of cell aggregates, resembling microvilli of the intestinal mucosa. The epithelial cells' cytoplasm is slightly eosinophilic, the cells are located close to each other, which indicates that intercellular contacts are preserved. Attention is drawn to the presence of slight cellular polymorphism, changes in the ratio of the cytoplasm and the nucleus sizes. This is manifested by the presence of different sizes cells with unevenly colored cytoplasm, oval or grumose hyperchromic nuclei. In some groups of epithelial cells there is an increase in the cytoplasm area with the cell boundaries vanishing.

In this case, it becomes less eosinophilic, reflecting the phenomenon of vacuolar degeneration, which is manifested by the emergence of numerous different sizes vacuoles, which sometimes completely fill the cytoplasm (fig. 1). Between the layers of cells throughout the slides, small granularity intensely stained with hematoxylin can be detected, immersed in a slightly eosinophilic or basophilic structureless material. Sometimes fine-granulated slightly basophilic material is found, which is apparently coagulated protein. Due to the peculiarities of obtaining the material and its processing, it is difficult to conclude on the type of epithelial cells, but they apparently belong to the intestinal epithelium, it is almost impossible to detect atypical cells due to the large amount of mucus. A feature of the studied cytograms is the absence of any inflammatory reaction signs. Lymphocytes, segmental leukocytes and macrophages were not detected throughout the slides.

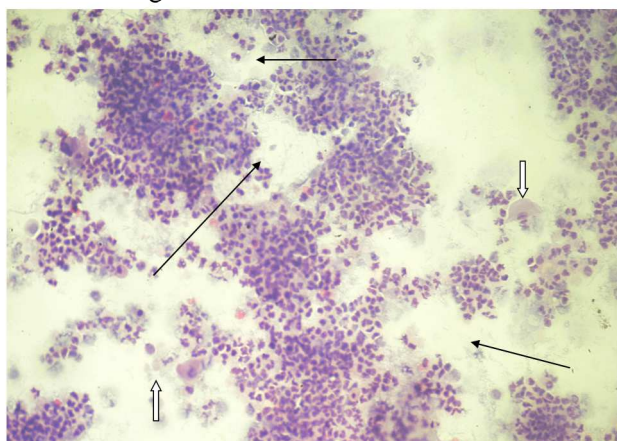


Fig. 1. Urine sediment cytogram features of patient K. one month after the surgery. Areas of epithelial cells with concentric cell aggregates between which there are large cells with light cytoplasm and small nucleus in the state of vacuolar degeneration (goblet cells) (arrows). Squamous epithelial cells (fancy arrows) (hematoxylin-eosin; x 120)

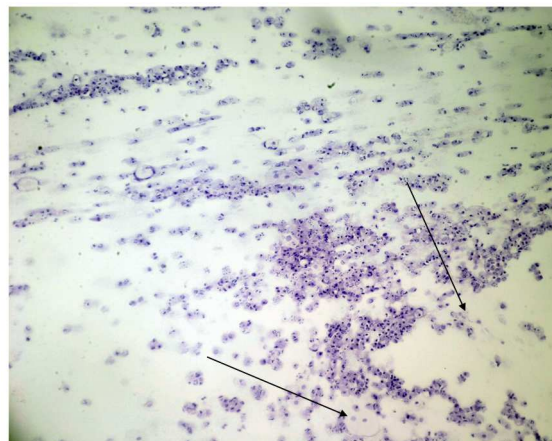


Fig. 2. Features of a urine sediment cytogram of patient L. 3 months after the surgery. Single epithelial cell complexes of different shapes and single cells diffusely distributed. Part of cells have oval and oblong shape. Groups of large cells, probably goblet (arrows) (hematoxylin-eosin; x 120)

One month after the surgery, single or small goblet cells complexes, different from epithelial cells by their much larger size, wide rim of slightly eosinophilic cytoplasm and light oval nucleus, can be detected in the slides. Noteworthy is the presence of the peculiar for these cells distinct border between goblet cells in the form of a distinct thin black stripe. Between the layers of epithelial cells against the background of homogeneous structurally weakly basophilic mass, isolated oval cells lying separately, which were apparently separated from the layers, are observed. The nuclei of such cells are small in size, deformed. The cytoplasm is basophilic.

Three months after the surgery, the urine sediment cytogram looks different. Instead of the large size epithelial cells layers occupying almost the entire field of view, even with a small magnification of the microscope, the cytogram looks reticular. Microscopically, it looks like an aggregate of small bundles or groups of differently sized epithelial cells with irregular shape. In this case, the groups and bundles of epitheliocytes interact. Cell-free space is left between the cells, filled either by unstructured mass, or by fine-granulated material, or by separate cells isolated from epithelial complexes, subjected to degeneration or necrosis (fig. 2). Part of the cells has a round, oval or spindle shape.

In the epithelial layers, some of the epitheliocytes have swollen cytoplasm (or in a state of vacuolar degeneration). In vacuolar degeneration, in the cell cytoplasm numerous, approximately the same size,

vacuoles are determined. It should be noted that the cytoplasm of epitheliocytes in some layers remains eosinophilic, in others - basophilic. The cells have intensely blue-colored cytoplasm of large size and irregular shape. In their cytoplasm large vacuoles are detected. Basophilia of the cytoplasm is most likely associated with mucoid aggregation.

Noteworthy is the presence of a cell aggregate similar to the tubular structures to which the bundles of loose connective tissue are attached. Apparently, these structures are preserved fragments of the intestinal villi.

A feature of urine sediment cytograms 3 months after the surgery is the presence of cell groups or single cells surrounded by a weakly basophilic material (mucin). Some observations show “shadows” of large cells. The latter are much larger than epitheliocytes, located in the form of single cells or small groups. Their cytoplasm is light and subjected to vacuolar degeneration. The nuclei are small, grumose. A distinct border of the cell in the form of a dark strip is observed. Apparently, such cells belong to the goblet ones. With a larger magnification of the microscope, it turns out that such “shadows” of cells are nothing else but goblet cells, which were subjected not only to vacuolar degeneration, but also to necrosis. This process is manifested by induration and basophilia of the deformed cell, karyolysis, and cytoplasm swelling.

This time period after the surgery is characterized by the fact that in some areas of the slide it is possible to detect signs of an acute inflammatory process. This is manifested in the cytogram by aggregates of lymphocytes, segmental leukocytes and eosinophilic leukocytes diffusely distributed among epitheliocytes in a small number. It is noted that near the leukocyte aggregations the most pronounced degeneration of epithelial cells is observed. Atypical urothelial carcinoma cells were detected in 1 patient, accounting for 3.8% ( $p \leq 0.01$ ), which was due to upper urinary tract cancer not diagnosed before the radical cystectomy.

Six months after the surgery, significant microscopic differences in the urine sediment cytograms are determined. First of all, it should be noted that the number of structural elements in the prints is small and difficult to determine, even scanning the entire area of the slide. In cases where the material is found, it is an aggregate of epithelial cells with a pronounced degree of degenerative changes, destruction and disintegration of the epithelial layer. In this case, small groups or single cells are found in a state of marked degeneration or necrosis. The preserved cells are rounded, spindle-like or oval in shape. In this case, the cytoplasm area is significantly increased in them, and they are flattened, pale. The nuclei of such cells are deformed and undergo pycnotic changes (fig. 3). Microscopically, phenomena of pycnosis are manifested by the reduced size of the nucleus, its hyperchromia, and its disintegration into different numbers of irregularly shaped basophilic fragments.

Some epitheliocytes resemble squamous epithelial cells. As with less durable observation after the surgery, in some places of the slide it is possible to find fragments in the form of a “tubular” structure, which is nothing else but a fragment of the villi.

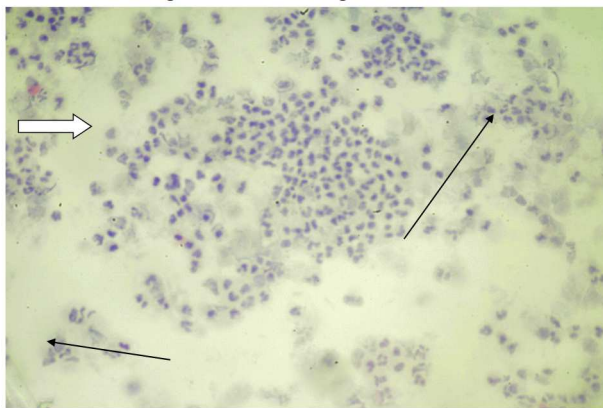


Fig. 3. Urine sediment cytogram features of patient L. 6 months after the surgery. Inflammatory response is preserved in the form of a small number of segmental leukocytes. Small fragments of epithelial flattened cells with preserved intercellular contacts (arrows) are identified. Between the epitheliocyte complexes there are structures resembling villi (arrow) (hematoxylin-eosin; x 120)

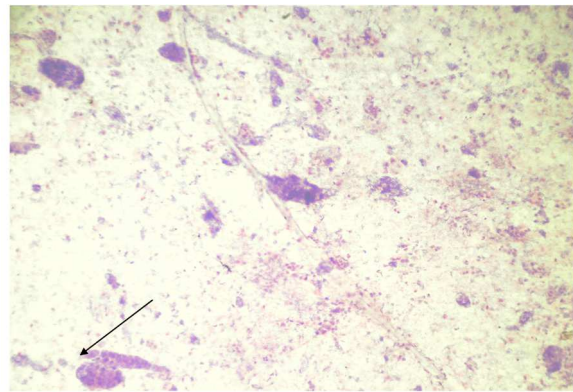


Fig. 4. Features of a urine sediment cytogram of patient L. one year after the surgery. In the heterogeneous fine-granulated slightly eosinophilic material, several necrotic-altered epithelial cell complexes with different shapes and basophilia degrees are detected. A preserved epithelial cell complex (arrow) is also determined (hematoxylin-eosin; x 120)

In some observations, fields of completely necrotic small cell aggregates or isolated cells are identified in the slides. They are intensely basophilic and have a fine-granulated structure. Diffusely distributed numerous erythrocytes can also be detected in the slide.

It should be noted that after 6 months in some places of the slide there are signs of inflammatory reaction, as evidenced by the detection of epithelial cells diffusely distributed between the layers or in the form of a small group of segmented leukocytes aggregation.

After 6 months, the inflammatory reaction intensity is significantly lower than that observed 3 months after ileocystoplasty. Eosinophilic leukocytes are virtually undetectable. There are no signs of inflammation at all in some places. Atypical urothelial cancer cells were detected in two patients, accounting for 7.69% ( $p \leq 0.05$ ), and it was due to the underlying disease recurrence and progressive growth into the neobladder.

Twelve months after the surgery, urine sediment cytograms are characterized by a small amount of structural elements found in cytological slides. Single unevenly distributed small epithelial cell aggregates are observed in the slides (fig. 4). Some of the cells forming the complexes are characterized by a small rim of slightly eosinophilic cytoplasm, and some of them are in a state of vacuolar degeneration or necrosis. Cells subjected to vacuolar degeneration have a wide rim of slightly eosinophilic cytoplasm, in which different size vacuoles are found. There are no cell borders.

Cells subjected to necrosis are intensely blue-colored structures seen as tubules of irregular shape and different size. They are surrounded by a fine-granulated heterogeneous mass, sometimes of a reticular structure. The reticular component often has a fibrous structure and consists of various lengths and thicknesses fibers intensely stained with hematoxylin in blue, which form aggregates of oblong shape and small size. It can be assumed that such formations are proteins that have undergone coagulation.

It should be noted that some isolated or small groups of cells resemble squamous epithelial cells, as they have a wide rim of cytoplasm, which have sufficiently intense eosin staining. In some observations, single diffusely distributed eosinophilic leukocytes can be detected in the slides, indicating that there is an allergic reaction. However, it is unknown which of the underlying urinary tract parts it takes place in. Atypical cells in the study group were not observed within a year, possibly due to the early control of the cellular elements in the urine sediment.

Cytograms of urine sediment 24 and 12 months after the surgery cytologically practically do not differ in features of their structure. In such cases, it is seldom possible to find single aggregates of epithelial cells located at a considerable distance from each other. Complexes of epithelial cells are immersed in heterogeneous, unstructured material of pink color, in which particles of irregular shape and different size intensely colored with hematoxylin are observed. Some of them have a narrow rim of weakly eosinophilic cytoplasm and resemble lymphocytes. Fragments of slightly fibrous basophilic material of unknown origin are sometimes identified. The fibers are oriented in parallel to each other, between them slit-like structureless space is defined.

The quantitative assessment in the field of view of the main cellular elements in the urine sediment of patients with artificial bladder showed a certain pattern in the cytological composition and is presented in table 1.

Table 1

**Dynamics of the neobladder urine cytological profile**

| Cell elements  | 1 month    | 3 months   | 6 months   | 12 months  |
|----------------|------------|------------|------------|------------|
| Epitheliocytes | 83.3±12.2% | 29.4±6.13% | 28.7±5.14% | 11.9±1.4%  |
| Goblet cells   | 7.6±2.12%  | 24.5±8.11% | 18.5±4.21% | 5.5±1.7%   |
| Leukocytes     | 6.53±3.1%  | 53.7±14.7% | 34.9±7.12  | 78.3±16.4% |
| Erythrocytes   | 2.57±2.6%  | 16.9±3.1%  | 17.9±18.5% | 4.3±1.2%   |

It should be noted that over time, the number of cellular elements in the urine decreases progressively, with the tendency to the epithelial cells reduction. Epitheliocytes in the first month - 83.3±12.2% - cover the entire field of view, being the dominant cellular component, exfoliating as a result of the urine toxic effect on the ileum wall. Three months later, the percentage ratio changed significantly with a smaller proportion of epithelial cells by 53.9% to 29.4±6.13% ( $p \leq 0.01$ ), with a progressive reduction to 11.9±1.4% in the 12th month of the study. In its turn, the highest level of goblet cells in the urine sediment is observed three months after the ileocystoplasty and is 24.5±8.11%, with a progressive tendency to decrease in dynamics. Leukocytes in their highest proportion are observed in the 3rd and 12th months and are 53.7±14.7% and 78.3±16.4%, respectively, characterizing the inflammation processes at these stages of the study. Erythrocytes in the highest percentage were observed in the 3rd and 6th months and made 16.9±3.1% and 17.9±18.5% respectively.

As a result, the study revealed a certain pattern of changes in the cellular composition of urine sediment after the surgery, depending on the time duration after the surgery. First of all, it should be noted that the structural features of cytograms to some extent reflect the dynamics of the processes that occur in the postoperative period.

Shortly after the surgery (1 month) in almost all slides and throughout the specimen under study large layers of epithelial cells belonging to the intestinal mucosa can be detected, as evidenced by the

histaarchitectonics of epithelial cell complexes (concentric location of cells in the small amount of stromal elements). Quantitative assessment of cytological data also revealed prevalence of epitheliocytes -  $83.3 \pm 12.2\%$ , which is consistent with the opinion of the researchers regarding the atrophy of the epithelial layer and the desquamation of the epithelium [2]. Meanwhile, the revealed structural changes reflect the process of the mucosal surface layers desquamation, mucin accumulation in the form of large basophilic homogeneous formations, degeneration of goblet cells, which preserve the cytoplasmic membrane, but lose intracytoplasmic inclusions. It is important to emphasize that in this period of time there are no microscopic signs of inflammatory reaction, which is manifested in the absence of lymphocytes, segmental neutrophils and eosinophilic leukocytes, plasma cells and macrophages in the slides. Quite pronounced inflammatory reaction is detected only 3 months after the surgery, its intensity is decreasing up to 6 months. Moreover, there is an acute reaction manifested by the presence of a large number of segmented neutrophil leukocytes and eosinophilic leukocytes. The presence of eosinophilic leukocytes indicates the presence of an allergic reaction that develops in this time period after the surgery. At the same time, the phenomena of vacuolar degeneration of epithelial cells, reduction in the number of cellular complexes, goblet cells and mucins, which is consistent with other researchers' studies [12]. In some observations, sediment shows deposits of calcium salts (calcificates) at the sites of degeneration and epithelial cells necrosis, reflecting, to some extent, the severity of degenerative changes in epithelial cells of the intestinal mucosa.

A few years after the surgery, the cytograms show: exceptionally small numbers of cells of unknown origin, coagulated proteins and crystals (possibly uric acid), and complete absence of an inflammatory reaction signs. Similar data were obtained by Pirola G.M. in their study of the ileum morphological changes [9].

The possibility of dynamic control of atypical urine cells permits the early detection of the underlying disease recurrence or the detection of urothelial carcinoma of another localization [8, 11]. Dynamic changes in the cytological composition of urine sediment reflect the processes of adaptation and rearrangement of the ileum mucous membrane to new conditions of existence and are manifestations of its contact with a new aggressive environment - urine.

### Conclusions

1. The revealed dynamics of structural changes in urine sediment after the surgery indicates that, in the presence of positive clinical results of the surgery, the processes of restructuring the epithelial lining in the intestinal fragment transplanted instead of the bladder, aimed at performing other functions, are completed.

2. The presence of single epithelial cells in the cytograms does not indicate the presence of the intestinal mucosa squamous metaplasia phenomena, predicted by some authors, as such cells may emerge as a result of the mucous membranes exfoliation in the urinal tract.

3. Based on the data obtained, we can assume the possibility of using the cytological study in the clinic to determine the dynamics of the process after surgical treatment, to determine the degree of the transplanted epithelium exfoliation, as well as to correct individual links in the process of the transplanted intestinal fragment's adaptation to the fundamentally new conditions of functioning.

4. Atypical cells in the urinary sediment were detected in 11.54% of patients, indicating this method of control as simple, non-invasive and specific for early diagnosis of local recurrence or primary upper urinary tract cancer.

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## Реферати

### ДИНАМІЧНІ ЗМІНИ КЛІТИННОГО СКЛАДУ ОСАДУ СЕЧІ АРТИФІЦІЙНОГО СЕЧОВОГО МІХУРА

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Метою роботи було оцінити динамічні зміни клітинного складу осаду артіфіційного сечового міхура. Виявлена динаміка структурних змін осаду сечі після оперативного втручання свідчить про те, що, при наявності позитивних клінічних результатів операції, завершуються процеси перебудови епітеліального вистилання пересаженного замість сечового міхура фрагмента кишечника, спрямовані на виконання інших функцій. На підставі отриманих даних можна припустити можливість використання в клініці цитологічного дослідження для встановлення динаміки процесу після оперативного лікування, виявлення ступеня ексфолюації епітелію пересаженного кишечника, а також корекції окремих ланок процесу адаптації в нових умовах функціонування пересаженного фрагмента кишечника, які принципово відрізняються.

**Ключові слова:** артіфіційний сечовий міхур, клітинний склад, адаптація.

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### ДИНАМИЧЕСКИЕ ИЗМЕНЕНИЯ КЛЕТЧНОГО СОСТАВА ОСАДКА МОЧИ АРТИФИЦИАЛЬНОГО МОЧЕВОГО ПУЗЫРЯ

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Целью работы было оценить динамические изменения клеточного состава осадка артіфіціального мочевого пузыря. Выведенная динамика структурных изменений осадка мочи после оперативного вмешательства свидетельствует о том, что, при наличии положительных клинических результатов операции, завершаются процессы перестройки эпителиальной выстилки пересаженного вместо мочевого пузыря фрагмента кишечника, направленные на выполнение других функций. На основании полученных данных можно предположить возможность использования в клинике цитологического исследования для установления динамики процесса после оперативного лечения, выявления степени эксфолюации эпителиа пересаженного кишечника, а также коррекции отдельных звеньев процесса адаптации в новых условиях функционирования пересаженного фрагмента кишечника, которые принципиально отличаются.

**Ключевые слова:** артіфіціальный мочевой пузырь, клеточный состав, адаптация.

Рецензент Старченко І.І.

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## RISK OF ADENOCARCINOMA IN BARRETT'S ESOPHAGUS

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The total of 7396 videoesophagogastroscopy cases were analyzed. The presence of metaplastic columnar epithelium of esophagus was found in 2910 patients (39.4%) at pathohistological examination. The gastric metaplasia was evaluated in 876 cases (11.9%), the specialized intestinal metaplasia without dysplasia - in 1970 (26.6%), the low-grade dysplasia - in 48 (0.65%), the high-grade dysplasia - in 16 (0.22%). Esophageal adenocarcinoma was evaluated in four patients (0.05%, CI 0.01 - 0.12%). Low probability of esophageal adenocarcinoma formation in all types of metaplasia was demonstrated. Only the presence of dysplasia of metaplastic epithelium should cause increased alertness for the occurrence of esophageal adenocarcinoma. Exaggerated value of Barrett's esophagus may result in additional traumatization of mucosa, increase the risk of bleeding and stenosis.

**Key words:** Barrett's esophagus, metaplasia, dysplasia, esophageal adenocarcinoma.

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Barrett's esophagus (BE) is the condition in which metaplastic columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus. BE predisposes to cancer development. In addition to Barrett's mucosa, a source of esophageal adenocarcinoma (EAC) may be cardiac or submucosal glands. Estimates of the prevalence of BE in the general population have varied widely from 0.4 to more than 20 percent, although the large majority of cases go unrecognized [12, 13].