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ORIGINAL ARTICLE

CLINICAL AND MORPHOLOGICAL FEATURES OF BLADDER CANCER COURSE IN HPV-INFECTED PATIENTS

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ABSTRACT

Purpose of the study. To study the histological type, grade of tumor differentiation in patients with primary and recurrent clinically non-muscle-invasive bladder cancer (NMIBC) with highly carcinogenic human papillomavirus (HPV) infection.
Patients and methods. Formalin-fixed and paraffin-embedded bladder tumor tissue samples have been studied in 159 patients who underwent transurethral resection (TUR) of the bladder, for the presence of HPV DNA. To detect, quantify and differentiate DNA of HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 genotypes in the samples, the AmpliSense® HPV HRC genotype-titer-FL was used. The result of the study was taken into account when the amount of DNA of the β-globin gene was at least 1000 copies per reaction. In order to statistically analyze our data we used the Fisher exact test and also calculated the odds ratio (OR) and 95 % CI.
Results. According to the results of the study, out of 159 patients, high-risk HPV DNA was detected in the tumor tissue in 59 (37.1 %), of which HPV type 16 was found in 52 patients (89.4 %), HPV 18 was detected in 4 patients type (6.7 %) and type 35 in 3 (5.08 %). In a morphological study of the tissues of HPV-positive patients, the grade of tumor differentiation was G2 in 18 cases (30.5 %), G3 in 37 blocks, and G1 was detected only in 4 cases (6.7 %). In the presence of HPV, the chance of detecting a stage G3 tumor increases by 4.3 times. According to the received data, we can assume that there is a close relationship between detection in HPV patients of high-risk genotypes with moderately differentiated and low-differentiated forms of bladder cancer.
Conclusion. this study may indicate that HPV infection affects the grade of tumor differentiation, and this, in turn, may allow the use of the HPV test to assess the nature of the development of relapse and/or progression of the disease.

Keywords: bladder cancer, human papillomavirus, urothelial carcinoma, transurethral resection of the bladder

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ОРИГИНАЛЬНАЯ СТАТЬЯ

КЛИНИКО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ТЕЧЕНИЯ РАКА МОЧЕВОГО ПУЗЫРЯ У ВПЧ-ИНФИЦИРОВАННЫХ БОЛЬНЫХ

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РЕЗЮМЕ

Цель исследования. Изучение гистологического типа, степени дифференцировки опухоли, у больных первичным и рецидивирующим клинически немышечно-инвазивным раком мочевого пузыря (НМИРМП) при инфекции вирусом папилломы человека (ВПЧ) высокого канцерогенного риска.

Пациенты и методы. Изучены образцы фиксированных в формалине и залитых в парафин тканей опухолей мочевого пузыря у 159 пациентов, перенесших трансуретральную резекцию (ТУР) мочевого пузыря на наличие ДНК ВПЧ. Для выявления, количественного определения и дифференциации ДНК ВПЧ 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 генотипов в образцах использовали набор реагентов «АмплиСенс® ВПЧ ВКР генотип-титр-FL». Результаты учитывались при количестве ДНК β-глобинового гена не менее 1000 копий на реакцию. Для проведения статистического анализа полученных нами данных, мы использовали точный критерий Фишера, а также рассчитывали отношение шансов (OR) с 95 % ДИ (CI).

Результаты. По результатам исследования из 159 пациентов ДНК ВПЧ высокого риска была обнаружена в ткани опухоли у 59 (37,1 %), из них ВПЧ 16 типа у 52-ти больных (89,4 %), у 4-х выявлен ВПЧ 18 типа (6,7 %) и 35 типа у 3-х (5,08 %). При морфологическом исследовании тканей ВПЧ-позитивных пациентов степень дифференцировки опухоли в 18 случаях (30,5 %) являлась G2, в 37 блоках- G3 и лишь в 4 случаях (6,7 %) выявлен G1. При наличии ВПЧ повышается в 4,3 раза шанс обнаружения опухоли стадии G3. По полученным данным мы можем предположить, что имеется тесная связь между выявлением у пациентов ВПЧ генотипов высокого риска с наличием умеренно дифференцированных и низкодифференцированных форм рака мочевого пузыря (РМП).

Заключение. Данное исследование может свидетельствовать о том, что ВПЧ инфекция влияет на степень дифференцировки опухоли, а это в свою очередь, может позволить использовать ВПЧ-тест для оценки характера развития рецидива и/или прогрессирования заболевания.

Ключевые слова: рак мочевого пузыря, вирус папилломы чело века, уротелиальная карцинома, трансуретральная резекция мочевого пузыря

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Информированное согласие получено от всех участников исследования.

Финансирование: финансирование данной работы не проводилось.

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTODUCTION

Bladder cancer (BC) is one of the most common pathological conditions, which ranks 7th among men and 17th among women in the world. In Russia, this disease ranks 9th among the male population (4.6 %), and 16th among women population. In recent years, the incidence of bladder cancer has increased, however, the widespread use of visualization diagnostic methods allows diagnosing bladder cancer in 75 % of cases at stage I-II of the disease. Nevertheless, this disease is a growing public health problem due to the frequent recurrence and progression of the tumor process [1].

Urothelial carcinoma, which accounts for about 90 % of all cases of bladder cancer, is so far the most common histological type worldwide. The stratification of bladder cancer can be binary, based on the depth of penetration, i. e. muscle-invasive (MIBC) and non-muscle-invasive (NMIBC) bladder cancer. NMIBC accounts for about 75 % of newly diagnosed urothelial cell carcinoma of the bladder [2]. Due to the high mitotic activity of urothelial bladder carcinoma (UBC), despite the radical transurethral resection of the bladder tumor and adjuvant intravesical therapy, after performing transurethral resection of the primary tumor in NMIBC, relapse occurs in 30–60 % of cases [3].

Well-known risk factors for bladder cancer include cigarette smoking, several occupations associated with exposure to aromatic amines (for example, industrial production of dyes), cyclophosphamide and frequent use of the analgesic phenacetin. Possible carcinogens for bladder cancer are parasitic (schistosomiasis) and bacterial agents (nonspecific urinary tract infections, gonorrhea), as well as viral infections such as human papillomavirus (HPV) [4; 5].

One of the most common sexually transmitted infections is HPV. During the examination of patients in medical centers of the Russian Federation (RF) in 2019 the HPV deoxyribonucleic acid (DNA) was discovered in 5015 (39 %) of 12946 examinees. It was also noted that 3509 patients had one type of HPV, and 1957 patients had several types of HPV, and among 5015 people 8584 had HPV of different types [6]. There are more than 200 different types of HPV affecting human mucous membranes and skin, of which 14 types belong to the high-risk group (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73). Those are detected in 98 % of cases of cervical, vaginal and vulvar cancers. HPV 6 and 11 are the most common cause of genital warts, whereas HPV types 16 and 18 lead to the development of intraepithelial neoplasia and cervical cancer [7]. HPV is also a well-known mucosotropic carcinogen and a common cause of cancer in the anogenital region.

HPV DNA replication occurs only in the cells of the basal layer, and in the cells of other layers of the epidermis, viral particles only persist, including the transition zones of the multilayer epithelium into the cylindrical one. This process is controlled by virus proteins, which disrupt the normal process of cell differentiation, leading the death of the cellular nucleus and, as a result, the alteration of the epidermis.

A feature of HPV is its ability to persist in the human body for a long time, affecting only the basal layer of the epithelium, while it does not penetrate into the blood. The virus resides in the form of an episome in the cell, and due to this infection course is often benign [8].

When comparing groups of HPV-positive and HPV-negative patients, higher cellular anaplasia was found in people with BC infected with HPV, due to which primary cancer is more often HPV-positive in contrast to recurrent [9].

According to a study by the Department of Human Pathology of Wakayama Medical University (Japan), using the in situ miRNA hybridization (RISH) RNAscope method, high-risk HPV E6/E7 mRNA was analyzed in shear of BC tissues filled with paraffin. Low-grade and high-grade urothelial cancer (UC) were detected in 61 (26.8 %) and 167 (73.2 %) cases, respectively. Noninvasive UC was the most common tumor (39.5 %, including 37.3 % pTa and 2.2 % PTIs), followed by invasive pT1 (21.9 %), pT2 (18.0 %), pT3 (11.4 %), pT4 (3.1 %) and metastatic tumor (6.1 %) [3].

Despite the experimental and theoretical data accumulated up to date, many oncogenic properties of HPV, their involvement in the pathological process and influence on the processes of relapse, progression of bladder cancer remain poorly understood.

Purpose the study: to study the histological type and the grade of tumor differentiation in patients with primary and recurrent clinically muscle- noninvasive BC with HPV infection of high carcinogenic risk.

PATIENTS AND METHODS

Our study involved patients with confirmed BC (*n* = 159) who underwent transurethral resection (TUR) of the bladder. The average age of the patients was 63.7 years ± 11.6 years. Among them 136 men and 23 women were. All patients (*n* = 159) included in the study had a preoperative clinical stage cT1N0M0. The criteria for inclusion in the research work were the following: morphologically confirmed non-muscle-invasive urothelial bladder cancer in the clinical stage cT1N0M0, where can be performed transurethral resection. The patients voluntary participation in all stages of the study was confirmed by informed consents they have signed. We also put forward criteria according to which we excluded patients from the study, and those are: the presence of non-urothelial BC; the presence of therapeutic or psychiatric reasons that could potentially challenge the participation in the study; pregnancy or lactation; inability to perform transurethral resection of BC. Transurethral resection of the bladder for primary BC was performed in 97 patients, and 62 patients underwent surgery for recurrent BC.

HPV status of patients was determined by PCR test. The presence of HPV DNA was determined in tumor tissue, which was fixed in formalin and filled with paraffin (FFPE tissue). Before the analysis, the paraffin was removed with xylene and 96 % ethanol. HPV DNA of high cancerogenic risk was determined (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 types) by PCR. The cross-binding of formalin to DNA was eliminated by incubation at a temperature of 90 °C after cleavage with proteinase. The result of the study was taken into account when the amount of DNA of the β-globin gene was at least 1000 copies per reaction. To carry out statistical analysis of the data obtained by us, we used the Chi-square Criterion with the Yates correction, the exact Fisher criterion, and also calculated the odds ratio (OR) with 95 % CI. To assess the strength of the relationship between the risk factor and the histotype, stage or relapse, a normalized value of the Pearson coefficient or Kramer's criterion V was used.

STUDY RESULTS

According to our study, in samples from 159 FFPE DNA blocks, HPV of high oncogenic risk was detected in tumor tissue in 59 patients (37.1 %). HPV type 16 of those was present in 52 patients (89.4 %), HPV type 18 (6.7 %) in four patients, and HPV type 35 was detected in three patient (5.08 %). During morphological examination of the tumor tissue of HPV-positive patients, only 43 (72.6 %) patients had a typical transitional-cell BC, and 15 (24.4 %) patients had squamous cell differentiation and 1 (1.7 %) patient had micropapillary BC (Table 1). The last two histological variants refer to tumors of high malignant potential (high-grade), which is a poor prognostic criterion. While in HPV-negative patients, 96 (96 %) patients had a typical transitional cell BC and 4 (4 %) patients had squamous cell differentiation

Evaluation of the significance of histotype differences depending on the exposure to risk factor (HPV) showed that statistically significantly the absence of HPV infection leads to the development of transitional cell BC (Chi-squared criterion with Yates correction = 15.994, $p < 0.001$; Fisher's exact

Table 1. Urothelial cancer morphological type depending on HPV presence

	HPV-positive BC patients (*n* = 59)	HPV-negative BC patients (*n* = 100)
Transitional cell BC (*n* = 139)	43 (72.9 %)	96 \ 100 (96 %)
Squamous cell BC (*n* = 19)	15 (25.4 %)	4 \ 100 (4 %)
Miscropapillary BC (*n* = 1)	1 (1.7 %)	Not detected

criterion (bilateral) = 0.00004, $p < 0.05$). At the same time, the strength of the relationship between the risk factor and the histotype was relatively strong (the normalized value of the Pearson coefficient = 0.451).

Histological examination of the tumor tissue of HPV-positive patients according to the degree of tumor differentiation obtained the following results: G2 was detected in 18 cases (30.5 %), G3 – in 37 blocks (62.7 %) and only in 4 cases (6.7 %) G1 was detected (Table 2)

The statistical analysis showed that the presence of HPV reduces the chance of detecting a tumor of stage G1 (Lower limit, 95 % CI 0.140 Upper limit 95 % CI (CI) 1.427) and G2 (Lower limit 95 % CI 0.161. Upper limit 95 % CI 0.629). In the presence of HPV the chance of detecting a G3 stage tumor increases by 4.3 times (The lower limit is 95 % CI 2,180, the upper limit is 95 % CI 8,578), according to the obtained data, we can assume that there is a close relationship between the detection of high-risk HPV genotypes in patients with the presence of moderately differentiated and low-differentiated forms BC.

We also found that HPV does not significantly affect the development of grade G1, but affects the development of grade G2, as well as G3 (Fisher's exact criterion (bilateral) = 0.00003, $p < 0.05$).

In the structure of patients, recurrent HPV infection was detected more often (in 46.8 % of cases) than in patients with primary BC (in 30.9 % of cases) (Table 3).

According to the criteria for assessing the significance of differences in outcomes, our value (4.07) exceeds the critical one, which means that based on the application of Pearson's criterion $\chi 2$, the null hypothesis about the absence of a statistical relationship between the studied risk factor and the outcome can be rejected at a critical significance level of 5 % ($p = 0.044$). At the same time, the value of the Yates-adjusted $\chi 2$ criterion is 3.419, which is less than the critical value (3.841), which means that we cannot reject the null hypothesis about the absence of a statistical relationship between the risk factor and the outcome ($p = 0.065$). It is also shown that there is a weak link between the development of relapse of BC and HPV infection (Kramer's criterion V = 0.160).

However, an analysis of the effect of HPV infection on disease recurrence when calculating the odds

Table 2. The quantitative relations among HPV-positive and HPV-negative morphologically confirmed BC cases of different tumor grades of differentiation

	HPV-positive BC patients (*n* = 59)	HPV-negative BC patients (*n* = 100)
G1 (person)	4 (6.8 %)	14 (14 %)
G2	18 (30.5 %)	58 (58 %)
G3	37 (62.7 %)	28 (28 %)

Table 3. HPV status of the patients with primary and recurrent BC

	HPV-positive BC patients (*n* = 59)	HPV-negative BC patients (*n* = 100)
Primary BC (*n* = 97)	30 (30.9 %*)	67 (69.1 %*)
Recurrent BC (*n* = 62)	29 (46.8 %**)	33 (53.2 %**)
G3	37 (62.7 %)	28 (28 %)

Note: * – out of all patients with primary BC, ** – out of all patients with recurrent BC.

ratio with a 95 % confidence interval showed that HPV infection increases the chances of relapse by 2 times (Odds Ratio (OR) = 1.963, the standard error of the odds ratio (S) = 0.336, the lower limit 95 % CI = 1.015, the upper limit 95 % CI = 3.793).

After pathomorphological examination of the surgically removed material migration of the stage from clinical preoperative T1 to stage T2 in the postoperative material in HPV-positive patients with BC was observed 4.5 times more often (13.5 % of cases) than in HPV-negative patients (3 % of cases of BC), (Odds ratio (OR) = 5.072, S = 0.699, lower limit 95 % CI = 1.289, upper limit 95 % CI = 19.951) (Table 4).

Statistical analysis also showed the presence of an average strength of the relationship between the development of stage T2 and the presence of HPV infection (Kramer's Criterion V = 0.201). At the same time, the stage of the disease statistically significantly depended on the presence of HPV (Chi-squared with Yates correction = 4,890, p = 0.028).

DISCUSSION

Many scientists believe that HPV type 16 is often actually involved in the process of BC formation. HPV-affected tumor cells are able to influence the microenvironment, causing tumor recurrence from normal urothelial cells that were in close proximity to the area of the removed tumor. The direct effect on the HPV microenvironment of an infected tumor during its removal may further contribute to a prognostic factor [9].

HPV infection in most cases is cured spontaneously. In other cases, with the persistence of a high-risk virus, the risk of malignant neoplasm increases.

The confirmation of a specific type of HPV is necessary because different types of this virus have different potential to participate in carcinogenesis: oncogenic types of HPV are 16 and 18 for instance. The detection of several types of virus is a negative outcome and a more severe course of the disease with a high risk of persistence.

Given the contradictory nature of the literature data on the role of human papillomavirus in the pathogenesis of bladder cancer, we sought to investigate the frequency of their involvement in a cohort of patients with BC of varying degrees of invasion and differentiation. DNA was determined in 159 paraffin blocks for the presence of human papillomavirus. (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 types) of high oncogenic risk were determined by real-time PCR. Due to the limits of analytical sensitivity, our data cannot exclude the presence of extremely low levels of HPV16 or HPV18 in bladder tumors. Another factor proposed to explain the differences in the prevalence of bladder tumors is that the virus may not infect all parts of the tumor tissue in the same way. Thus, if the samples are not taken from an infected area, the test may give a false negative result. Similarly, contamination during sampling can lead to false positive results [5].

Out of 59 HPV positive results, histological examination revealed squamous cell differentiation of the tumor in 15 (25.4 %). This type of differentiation often indicates poor sensitivity to radiation and systemic chemotherapy. HPV infection was also detected in a single patient with micropapillary BC. One of the aggressive variants of the morphological component is micropapillary, and due to the low degree of cell differentiation and invasion into the muscle layer, the five-year survival rate in this variant of BC is 51 %. Of 59 HPV-positive patients, 37 (62.7 %) had a low degree of differentiation, 18 (30.5 %) had a moderate degree, and only 4 (6.8 %) had a high degree of differentiation.

It should be noted that in all patients with a positive HPV test, a low viral load was detected on average 2.1 ± 0.8 lg HPV\$10^5$ × β-globin, which we explain by the fact that all HPV tests used to date have been

Table 4. Postoperative stages of BC patients following the TUR of the bladder

	HPV-positive BC patients (n = 59)		HPV-negative BC patients (n = 100)	
Stage before the surgery/ number of patients	T1 (n = 59)	T2 (n = 0)	T1 (n = 100)	T2 (n = 0)
Stage after the surgery/ number of patients	T1 (n = 51, 86.4 %)	T2 (n = 8, 13.5 %)	T1 (n = 97, 97 %)	T2 (n = 3, 3 %)

validated for the cervical epithelium and the viral load is estimated due to the severity of cervical intraepithelial neoplasia. Clinically significant for cervical cancer and cervical intraepithelial neoplasia is the load from 3 to 5 lg 10^5 × β-globin, a high probability of developing cervical cancer is observed with an amount of more than 5 lg 10^5 × β-globin. At the same time, the assessment of viral load in bladder tumors has not been determined.

Thus, we found HPV DNA in tumor tissue in patients with a low or moderate degree of tumor differentiation, which is consistent with the literature data and may indicate an unfavorable course of the disease, as well as the possibility of using this relapse prediction test after complex treatment.

Previously published studies have shown the important role of HPV infection and the development of various types of malignant neoplasms, including cancer of the cervix, vagina, vulva, oropharyngeal zone, anogenital cancer. HPV type 16 is a papilloma virus with the highest oncogenic risk and is found in about 55–60 % of cases of cervical cancer. HPV type 18 is the second most oncogenic papilloma virus, which is found in about 10–15 % of cases of breast cancer [10].

CONCLUSION

According to the given study, in HPV-positive patients with a clinically diagnosed non-muscle-invasive BC, migration of the stage up to T2 was observed 4 times more often than in HPV-negative patients. At the same time, the prevalence of HPV in tumors of low and moderate malignancy was 93.2 %. Our results indicate a link between HPV infection and a lower degree of differentiation and a higher stage of the tumor process, as well as aggressive forms of urothelial cancer (squamous cell, micropapillary variants). Thus, this study may indicate that HPV infection affects the degree of tumor differentiation, and this, in turn, may allow the use of an HPV test to assess the nature of relapse and/or further progression of the disease.

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