

ADJUVANT CHEMOTHERAPY AND RECURRENCE FACTORS NON-INVASIVE BLADDER CANCER

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Abstract

Factors predicting the recurrence of bladder cancer play an important role in predicting the course of this disease. At the moment, it is customary to use prognostic factors EORTC and CUETO, but we have analyzed other prognostic factors. As a result of regression analysis for 12 months of follow-up, the following factors confirmed their prognostic significance: age, number of tumors, previous recurrence, category T, category G, Factor (Tumor basis), Factor (Recurrence in the first 6 months). Thus, it was found that the longer the follow-up of patients with non-invasive bladder cancer, the more prognostic factors we can detect, and therefore it is advisable to perform this study in the future.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Keywords: *bladder cancer, chemotherapy, prognostic factors, relapse*

Introduction

Bladder cancer is the second most common cancer of the genitourinary system after prostate cancer [1]. Importantly, 75% of newly diagnosed bladder cancers are non-invasive forms of bladder cancer [2].

In order to predict the course of bladder cancer - the urological community decided to use scales and tables of the European Organization for the Study and Treatment of Cancer (EORTC), which was based on 6 clinical and histological factors: tumor number, tumor diameter, recurrence rate, category T, class G and carcinoma in-situ [3].

In turn, the Spanish Group on Oncological Urology Club Urológico Español de Tratamiento Oncológico (CUETO) has created its own scale for assessing the course of NMIBC, which is based on 7 prognostic factors (sex, age, previous recurrence rate, number of tumors, category T, concomitant carcinoma in situ, the degree of malignancy of the tumor) and coincides with the EORTC scale [4].

The aim of the study. To analyze the effectiveness of prognostic factors for the recurrence of bladder cancer in patients with non-invasive muscular bladder cancer of low and medium risk group.

Materials and methods

The study included 161 patients, all patients were examined, treated and underwent dispensary at the clinic of the Institute of Urology of the National Academy of Medical Sciences of Ukraine in the period from 2013 to 2021. The youngest patient was 21 years old, the oldest 89 years old. The average age was 59.4 years. The ratio between men and women was 9: 3.4.

The criterion for inclusion of patients in the study was their attitude to low or medium risk (urothelial carcinoma stage Ta, T1; histologically class G1, G2, no CIS, total score on the EORTC scale maximum 9 points), no previous intravesical instillation with chemotherapy or BCG vaccine.

Exclusion criteria for the attitude of patients to high or ultra-high risk groups, the presence of muscle invasion in patients, stage T2 - T4, histological class G3, G4, the presence of previous

instillations of BCG vaccine, lack of clear information on previous intravesical instillation chemotherapy.

All patients underwent transurethral resection of the bladder tumor as the first stage of treatment. 124 patients out of 161 in the postoperative period underwent a course of instillation into the bladder of chemotherapeutics such as Doxorubicin, Epirubicin, Epirubicin in combination with Dimethyl sulfoxide. In the process of dispensary supervision, patients underwent control cystoscopies at 3, 6 and 12 months after the primary transurethral resection. Cystoscopic examinations revealed the presence or absence of recurrence of the disease. Thus, data from all patients were collected into a single database and analyzed for factors in the prognosis of recurrence of bladder cancer.

Combining the prognostic factors EORTC and CUETO it was found that 5 of them are the same - the number of tumors, the frequency of previous recurrences, category T, class G, Carcinoma in-situ, 1 factor EORTC - the diameter of the tumor, which is not in CUETO, and 2 factors CUETO (gender and age), which are not in the EORTC. In addition to the 8 factors EORTC and CUETO, based on literature data and our own experience - we have selected additional factors that we believe are important for predicting the progress of MNRSM.

During the collection of anamnesis we selected the following prognostic factors: hematuria in the anamnesis, pain over the womb, concomitant oncological disease, oncology in the anamnesis, diabetes mellitus, work in the chemical industry.

The following prognostic factors were important during the additional examination of the patient: the presence of enlargement of the renal heart rate according to ultrasound, anemia (blood hemoglobin level), creatinine level, urea level, blood type, rhesus factor; specific gravity of urine, leukocyturia, erythrocyturia, bacteriuria, erythrocyte sedimentation rate.

At the stage of transurethral resection, we selected the following prognostic factors: tumor location (right wall, left wall, apex, bottom, vesical triangle, above the eye, under the eye); the nature of growth (exophytic or endophytic), the basis of the tumor (creeping, leg). the size of the tumor leg (up to 1 cm, more than 1 cm).

The following factors were identified during the dispensary observation of patients: recurrence in

the first 6 months after the primary TUR, reTUR (whether reTur was performed), recurrence site (previous tumor site or new location), increased number of intravesical instillations.

Thus, in total, together with the EORTC and SUETO factors, 31 prognostic factors were selected, each of which has its own significance. The factor of carcinoma in situ was not taken into account, as all patients were from low and medium risk groups who did not have carcinoma in-situ.

Results

In order to filter the most important factors that could predict the risk of disease recurrence, the method of "Random forest" was used [5]. The most important factors are shown in Table 1.

In order to assess the risk of disease recurrence, as well as to confirm the results of the method "Random forest", we used the method of binary logistic regression. Logistic regression uses the maximum likelihood method, which maximizes the probability of classifying the observed data into a certain category using regression coefficients [6].

The predictive capacity of the model was 83%. The results of the binary logistic regression method are shown in Tables 2, 3 and 4.

Table 2 shows that statistically significant prognostic factors for recurrence during the first 3 months were: age, previous recurrence. Thus, at the age of above 60 years, the probability of recurrence after 3 months is 1.2 times higher when there were previous relapses than if there were none. With a previous recurrence, the patient is 1.5 times more likely to have a recurrence than if the patient had no recurrence.

According to Table 3 - in the period from 4 to 6 months, in addition to the previous 2 factors, 3 more factors were identified - the number of tumors, tumor base and factor 4 (recurrence in the first 6 months after the primary TUR). Therefore, patients with more than one tumor have a 1.4-fold higher risk of recurrence in the first 6 months than patients with one bladder tumor. Factor 2 (the basis of the tumor) has shown its importance, as the risk of recurrence in the first 6 months is 1.2 times higher than in the case of a leg tumor, factor 4 proved that is the patient has a recurrence of the disease in the first 6 months after the initial

TOUR, the probability of recurrence is 1.4 times higher than if there was no recurrence of the disease in the first 6 months.

Table 4 shows the factors identified during the 12 months of follow-up. Therefore, we added 2 new factors - category T and class G. Regression data show that patients with primary T1 tumor have a 1.4 times higher risk of recurrence than patients with primary tumor Ta, and if present in the primary tumor G2 risk of recurrence is 1.4 times greater than in G1.

Discussion

Our study used significantly more prognostic factors (31 factors) than the EORTC classification (5 factors) and the SUETO classification (6 factors). The difference between the integrated systems EORTC, SUETO and the lower study was that both EORTC and SUETO patients were of low, medium, high and ultra-high risk, while our study included only low and medium risk patients, and therefore such a prognostic factor as a concomitant carcinoma in situ we have not included in the study. Another difference is that in our study there were no patients receiving intravesical instillation of MMC or BCG, whereas EORTC patients received MMC and patients of the SUETO study had intravesical instillation of BCG. In the EORTC and CUETO studies, there is no evidence that prognostic factors become significant over time, as demonstrated by our study.

Conclusions

Each of the studied prognostic factors of bladder cancer, as well as their combination are of great importance in predicting the course of bladder cancer. Thus, for 12 months of follow-up, the following factors confirmed their prognostic significance: age, number of tumors, previous recurrence, category T, category G, Factor 2 (Tumor basis), Factor 4 (Recurrence in the first 6 months). Importantly, that the significance of prognostic factors is manifested with the time of observation : the longer the observation time, the greater the number of prognostic factors for recurrence of bladder cancer can be detected. These data suggest that the longer the follow-up of patients with non-invasive bladder cancer, the more prognostic factors we can detect, so it is advisable to conduct this study in the future.

Acknowledgments

The authors declare that there are no conflicts of interest.

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Table 1. The most important factors in the prognosis of PCM were identified with the help of “Random forest” algorithm

1	Age
2	Number of tumors
3	Tumor diameter
4	Previous relapse
5	Category T
6	Class G
7	Factor 1 (Erythrocyturia)
8	Factor 2 (Tumor basis)
9	Factor 3 (Tumor leg diameter)
10	Factor 4 (Relapse in the first 6 months)
11	Factor 5 (Increased number of instillations)

Table 2. The most significant factors in the prognosis of recurrence of PCM in the first 3 months

Factors	Coefficient regression	Statistical significance, p	Odds ratio
Age	-0,071	0,01	1,2
Number of tumors	-0,495	0,08	0,5
Tumor diameter	2,292	0,23	0,2
Previous relapse	18,042	0,04	1,5
Category T	2,555	0,058	0,1
Class G	0,743	0,12	0,3
Factor 1 (Erythrocyturia)	-0,428	0,34	0,7
Factor 2 (Tumor basis)	0,77	0,41	0,2
Factor 3 (Tumor leg diameter)	1,3	0,11	0,2
Factor 4 (Relapse in the first 6 months)	6,192	0,051	0,3
Factor 5 (Increased number of instillations)	-18,053	0,996	0,1
Constant	-23,384	0,994	0,1

Table 3. The most significant factors in the prognosis of recurrence of NMIBC in the first 6 months

Factors	Coefficient regression	Statistical significance, p	Odds ratio
Age	-0,061	0,01	1,3
Number of tumors	-0,44	0,04	1,4
Tumor diameter	2,345	0,16	0,2
Previous relapse	18,323	0,04	1,6
Category T	2,112	0,06	0,5
Class G	0,69	0,15	0,3
Factor 1 (Erythrocyturia)	-0,55	0,4	0,7
Factor 2 (Tumor basis)	0,68	0,03	1,2
Factor 3 (Tumor leg diameter)	1,4	0,07	0,2
Factor 4 (Relapse in the first 6 months)	6,292	0,02	1,4
Factor 5 (Increased number of instillations)	-17,899	0,4	0,3
Constant	-23,43	0,873	0,1

Table 4. The most significant factors in the prognosis of recurrence of PCM in the first 12 months

Factors	Coefficient regression	Statistical significance, p	Odds ratio
Age	-0,051	0,01	1,4
Number of tumors	-0,45	0,03	1,4
Tumor diameter	2,349	0,16	0,2
Previous relapse	19,323	0,04	1,6
Category T	2,42	0,03	1,4
Class G	0,79	0,04	1,4
Factor 1 (Erythrocyturia)	-0,65	0,4	0,7
Factor 2 (Tumor basis)	0,88	0,03	1,3
Factor 3 (Tumor leg diameter)	1,5	0,08	0,2
Factor 4 (Relapse in the first 6 months)	6,692	0,02	1,6
Factor 5 (Increased number of instillations)	-18,899	0,4	0,3
Constant	-24,63	0,678	0,1