

Original Article

Prognostic Value of Androgen Receptor Expression in Bladder Tumors

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HIGHLIGHTS

- The expression level of androgen receptors in healthy bladder tissues was slightly higher than in tumoral tissue, but the difference between the two groups was not statistically significant.
- Weak inverse correlations were observed between AST/ALT/ALP levels and androgen receptor expression but were not statistically significant.
- THE EXPRESSION LEVEL OF ANDROGEN RECEPTORS IN HEALTHY TISSUES WAS SLIGHTLY HIGHER THAN IN TUMORAL TISSUE.

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ABSTRACT

Introduction

The present study was conducted with the aim of investigating the prognostic value of androgen receptor expression in bladder tumors.

Methods

This study was conducted in the urology department of Imam Reza Hospital on male patients with bladder tumors between 2021 and 2023. In the patients included in the study, during the TURBT procedure, one sample of the tumor and one sample of the apparently healthy mucous membrane of the patient were sent to the pathology laboratory for examination of the expression of the androgen receptor. Then, all patient information, including demographic information (such as age), possible risk factors (such as smoking), tumor grade, tumor stage, and bladder tumor type, was recorded. Finally, the results were analyzed in SPSS software.

Results

A total of 47 male patients were included in the study, whose average age was 66.19 ± 12.63 years. All patients included in the study had TCC. In the grading, 35 patients (74.5%) were in high grade, and 12 other patients (25.5%) were in low grade. The average level of androgen receptor expression in healthy tissue and tumoral tissue was 17.34 ± 24.02 and 18.72 ± 28.35 , respectively. The amount of androgen receptors in healthy tissue was higher than in tumoral tissue, although this difference was not statistically significant (P -value=0.97). There was a weak inverse correlation between AST and androgen receptor, between ALT and androgen receptor, and between ALP and androgen receptor, but these were not statistically significant (P -value>0.05).

Conclusions

The expression level of androgen receptors in healthy tissues was slightly higher than in tumoral tissue, but the difference between the two groups was not statistically significant. Considering that the results of studies conducted in this regard are not consistent with each other, there is a need to conduct more studies to clarify the relationship between androgen receptors and bladder tumors.

Keywords: Bladder Tumor; Androgen Receptor; Prognosis

Introduction

One of the most prevalent cancers, bladder cancer affects men three times more frequently than women (1). Unknown is the cause of the disparities in incidence between the sexes (2-4). It is known that smoking tobacco and exposure to certain chemicals increase the risk of developing bladder cancer, but these risk factors alone cannot fully account for the higher incidence of bladder cancer in men (2, 5, 6). The gender disparity in bladder cancer incidence has also been linked to hormonal variations as a possible explanation. Studies on animal models of naturally occurring or chemically induced bladder cancer showed that hormonal manipulation altered the tumors' normal course and that androgen suppression generally resulted in better survival and more benign outcomes, indicating that androgens may play a role in the development of some bladder tumors and that their presence may promote tumor growth (5, 7). The role of sex steroid hormone receptors in the development of bladder cancer in humans, however, has received less research (2, 4, 8).

Patients with bladder cancer can be divided into subgroups based on prognostic factors (9). The most crucial subdivision is based on the stage and grade of the tumor, but we also believe that sex hormone receptor expression can have an impact on the choice of treatment and its approach (3). We were interested in learning more about whether targeting the androgen receptor can have a therapeutic effect on bladder cancer given the significance of androgen receptor roles in the initiation and progression of the disease. Here, we present the results of our investigation into the androgen receptor's presence in bladder transitional cell carcinoma. We also looked into the prognostic significance of androgen receptors (AR) in bladder cancer patients.

Methods

We studied specimens of Trans-urethral Resection of Bladder Tumor (TUR-BT) among 47 patients with bladder cancer treated at the urology department of Imam Reza Hospital from 2021 to 2023. Our inclusion criteria were male gender (to avoid background variable effects) and consent to participate in the study. And exclusion criteria were a history of chemotherapy, radiotherapy, and BCG therapy. The study was approved by the ethical committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1401.357).

The cancer diagnosis of the patient was made by a specialist doctor and matched with clinical and laboratory evidence, and the patient was treated (with a non-chemotherapy treatment method). We took urine cultures from patients and we performed this procedure on patients whose urine culture was negative. Samples for pathology came from biopsies performed during TUR-BT procedures from cancerous tissue and non-cancerous

regions of the bladder. The experimental procedures were conducted by the ethical standards of the Helsinki Declaration.

In pathology, the ratio of androgen receptors of biopsies with a special kit was checked. Grading was determined by a urologist and staging by pathology of biopsy. We registered demographic information of patients like age, and probably risk factors like smoking and tumor data like grading or type of it. This study was approved by the institutional review board of Mashhad University of Medical Sciences (ethical code 57.3IR.MUMS.MEDICAL.REC.1401). Informed consent to participate in the study was obtained from all subjects. The tools of our work in this research were the checklist related to recording the information of each sample and the kit for calculating the ratio of androgen in the tissue. The software SPSS version 26 was used to tabulate and analyze the data that were collected. Quantitative data was reported as a mean, standard deviation, and confidence interval, while categorical data was shown as frequency and frequency percentage. Using the T-student test and the ANOVA test to assess parametric variables, quantitative data were checked for normality using the Shapiro-Wilks test, which assumes normality at $P\text{-value}>0.05$. Nonparametric tests were utilized in cases where the results weren't normal. In this study, a significance level of 0.05 ($P\text{-value} 0.05$) was determined to be acceptable.

Kashiwagi et al., (8) reported the AR expression ratio of 20% and 57% in tumoral and normal healthy tissues respectively. By using the formula (for qualitative data in 2 groups), the above data, and by considering a relative error of 0.26 the sample size calculated 47 patients.

Results

This study included 47 histopathologically confirmed cases of urothelial carcinomas. The mean age was 66.19 ± 12.63 . 20 patients were smokers and 25 patients had an addiction history (Table 1).

All patients in this study had TCC. Thirty-five patients had high-grade tumors and 12 patients had low-grade tumors (Table 2).

AR expression in tumoral tissue was positive by an average of 28.25 ± 18.72 . Out of non-neoplastic tissue, the mean AR expression was 24.02 ± 17.34 . Overall, AR expression in non-neoplastic tissue was higher than in neoplastic tissue ($P\text{-value}=0.971$).

AR expression was similar between low- and high-grade tumors ($P\text{-value}=0.817$) and both groups had lower levels of AR expression than normal healthy tissue. Ta and T2-graded tumors had more ARs and CIS and T1 had lower levels ($P\text{-value}>0.05$) (Table 3).

When the patients were divided into two groups according to tumor grade, the expression of the receptor

Table 1. General variables

Variables	Frequency
Age (mean \pm SD)	66.19 \pm 12.63
Smoker, Num (%)	20 (42.6)
Addiction, Num (%)	25 (53.2)

in normal tissue was higher in both patients with low grade and patients with high grade compared to tumoral tissue. Despite this, there was no statistically significant difference between the expression level of the receptor in normal and tumoral tissue. (Respectively P-value>0.99 and P-value=0.84).

Discussion

Patients who were included in this study were all male and diagnosed with TCC. About three-fourths of them were graded as high. The most common stage was T2 by 27%, and after that, high-grade Ta by about 25%. Smoking and addiction were reported at 42% and 53%, respectively.

We studied the AR of normal and tumoral bladder tissues in cancerous patients; their incidence was similar. The results of studying them according to smoking were interesting: the median AR in non-smoker patients was zero, but for smoker patients, this was 20. This was not significantly different. AR expression in different stages of TCC was different; in T2, Ta high-grade, and Ta low-grade normal tissue had higher levels, but for CIS, T1 low-grade, and T1 high-grade tumoral tissue had higher levels. Even though the differences mentioned were not statistically significant. On the other hand, the grading of the tumor did not affect the AR level remarkably, and in both low- and high-grade tumors, normal tissue had more expression than tumoral tissue. Overall, normal tissue AR expression levels were slightly higher than tumoral tissue. And this study does not support the theory of AR's role in

Table 2. Tumors pathologic stage and grade

Pathologic stage	Frequency (percent)
Ta low grade	8 (17)
Ta high grade	12 (25.5)
CIS	2 (4.3)
T1 low grade	2 (4.3)
T1 high grade	10 (21.3)
T2	13 (27.7)
High grade	35 (74.5)
Low grade	12 (25.5)

the creation of bladder cancer.

The hypothesis of AR's role in bladder cancer originated from the fact that bladder cancer is more common in men than women. Some studies imagine functional roles for AR. For example, an in vitro study found that androgens can prevent BCG-induced IL-6 in AR-expressing cancers, and androgen withdrawal can neutralize this effect (10).

Wagih et al., studied the AR status of bladder urothelial carcinoma. IHC revealed that 58% of patients had positive AR expression. Despite the higher level of AR in high-grade tumors than in low-grade tumors, that was not significantly important. According to the different methodologies of the Wagih study, we cannot compare the results of the two studies. However, the conclusions were similar (11). Another study by Boorjian et al. studied bladder tumors in 49 patients. IHC showed that 53.1% of tumoral tissue and 86.5% of normal tissue expressed AR. High-grade tumors had fewer ARs; thus, they concluded the relationship between tumor invasion and loss of AR. The seeming contradiction between this study and ours can be explained by the low sample size of our study (12). Miyamoto et al., investigated AR, estrogen receptors, and their prognostic roles in bladder urothelial neoplasms.

Table 3. Healthy vs tumoral tissue features

Feature		Healthy Tissue Median (Interquartile Range)	Tumoral Tissue Median (Interquartile Range)	P-value
Smoking	Smoker	20 (0-30)	20 (0-45)	0.85
	Non-smoker	0 (0-20)	0 (0-30)	0.77
Addiction	Addicted	20 (0-20)	0 (0-25)	0.69
	Non-addicted	0 (0-30)	0 (0-30)	0.85
Grading	High grade	15 (0-30)	0 (0-30)	0.84
	Low grade	5 (0-27.5)	0 (0-30)	>0.99
Staging	Ta low grade	5 (0-30)	0 (0-22.5)	0.18
	Ta high grade	17.5 (0-27.5)	0 (0-27.5)	0.61
	CIS	0 (0-0)	20 (0-)	0.31
	T1 low grade	10 (0-)	45 (0-)	0.65
	T1 high grade	7.5 (0-22.5)	25 (0-55)	0.30
	T2	20 (0-50)	0 (0-25)	0.26

AR expression was positive in 80% of benign and 42% of malignant tissues. AR expression was lower in high-grade tumors. In the end, the authors found that loss of AR is associated with higher-grade and more invasive bladder tumors (13).

Mashhadi et al., evaluated clinical information and biopsy samples from 120 patients and 132 control subjects. None of the control people expressed AR, while for the cancerous group, this was 22%. Another finding of this study was that AR-positive patients had a worse prognosis than others (14). The most noticeable finding was that tumoral tissues expressed more AR than healthy tissues. The Nam et al. study revealed similar results; they said AR-positive patients had a higher probability of recurrence than AR-negative patients (15).

Some of the preclinical and epidemiologic studies suggest the possibility of an AR role in the differences in bladder cancer between men and women, and its expression can affect the prognosis of this cancer. A few researchers pointed out the signaling pathways of ARs as targets for treatment. However, evidence of AR effects in the creation and development of bladder tumors is not in the same direction. According to these, it seems that to achieve more reliable evidence for the prognostic value of AR in bladder cancers, more exact studies with a larger sample size should be designed and executed.

Conclusions

Despite higher levels of ARs in healthy tissue than tumoral ones, this was not statistically significant. Because of the disparity in information on this issue, more research is required.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethics statement

This study was approved by the institutional review board of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1401.357).

Data availability

Data will be provided on request.

Abbreviations

AR Androgen receptors
BCG Bacilli Calmette-Guerin

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