

ANDROGEN RECEPTOR POSITIVITY AND PROGNOSIS OF UROTHELIAL CARCINOMA

Karimbanakkal Edakkattu Abdul Jabbar¹, Gopalan Nair Rajan²

¹Assistant Surgeon, Primary Health Center, Mampad, Malappuram, Kerala.

²Additional Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala.

ABSTRACT**BACKGROUND**

Urothelial carcinoma is a common condition and comprises 7% of all cancers and 3% of all cancer deaths. Globally, the incidence of bladder cancer has been increasing. Smoking is associated with increase in urothelial carcinoma and is more common in male. The present study attempted to determine the usefulness of androgen receptor expression in these tumours as a prognostic marker.

The aim of the study is to determine the relation between Androgen Receptor (AR) positivity and grade of urothelial carcinoma. To determine the relation between AR positivity and grade individually and also in combination with the main outcome parameters namely, recurrence and survival in urothelial carcinomas.

MATERIALS AND METHODS

Details of patients were collected from case records of Urology and Pathology Departments. Patients were asked to come to Urology OPD and detailed history is taken and clinical examination done to find out current status. Paraffin blocks of the tissue were retrieved and sections stained with Haematoxylin and Eosin, and immunohistochemistry for androgen receptor and Ki-67 were done. Normal prostatic tissue is taken as control.

RESULTS

46 patients were included in the study. Most of the patients were in the age group of 60 to 69 years. Of them, 40 were males and 6 were females. Of the total patients studied, 33 cases were low-grade urothelial carcinoma and the remaining 13 were high-grade urothelial carcinoma. Out of 46 patients, 5 patients died, 9 patients showed recurrence, 3 patients showed AR positivity and 19 patients showed Ki-67 positivity more than 5%.

CONCLUSION

In this study, we could make out statistically significant relation between AR positive cases and Ki-67 positivity more than 5%. But, we could not make out any statistically significant association between grade, recurrence or survival with AR positivity of the carcinoma.

KEYWORDS

Androgen Receptor, Urothelial Carcinoma.

HOW TO CITE THIS ARTICLE: Jabbar KEA, Rajan GN. Androgen receptor positivity and prognosis of urothelial carcinoma. J. Evid. Based Med. Healthc. 2017; 4(56), 3421-3424. DOI: 10.18410/jebmh/2017/681

BACKGROUND

Urothelial carcinoma is a common condition and comprises 7% of all cancers and 3% of all cancer deaths. Globally, the incidence of bladder cancer has been increasing. Smoking is associated with increase in urothelial carcinoma and is still more common in males.^{1,2,3}

According to WHO 2004 classification, urothelial carcinoma has been divided into high-grade infiltrating urothelial and low-grade noninvasive urothelial neoplasias. Patients with low-grade tumours usually have a good prognosis in terms of disease-free survival, although they

recur with progression. But, invasive carcinomas are often life-threatening, despite aggressive management.⁴

Men have an approximately 3-fold higher risk of urothelial carcinoma than women, which indicates that sex hormones maybe involved in tumour development.⁵ There are previous studies done to determine if androgens and urothelial androgen receptors plays a role in bladder tumorigenesis.

Rahmani et al study found that androgen receptor expression was found to be associated significantly with tumour grades, age and sex suggesting that androgen receptor maybe used as prognostic markers in the treatment of urinary bladder carcinoma.⁶

Objectives of the Study

1. To determine the relation between androgen receptor positivity and grade of the urothelial carcinoma.
2. To determine the relation between androgen receptor positivity and grade individually and also in combination

*Financial or Other, Competing Interest: None.
Submission 01-07-2017, Peer Review 08-07-2017,
Acceptance 12-07-2017, Published 13-07-2017.*

Corresponding Author:

Dr. Gopalan Nair Rajan,

*Additional Professor, Department of Pathology,
Government Medical College, Kozhikode, Kerala.*

E-mail: rajanrema@yahoo.com

DOI: 10.18410/jebmh/2017/681



with the main outcome parameters namely, recurrence and survival in urothelial carcinoma.

MATERIALS AND METHODS

The study design is a retrospective cohort study. We retrieved 46 bladder specimens that we received during the period of three years from 2009 to 2011. All relevant patient data including contact details, clinical findings, investigations, status at discharge and further follow up details were collected from the case records of the Urology and Pathology departments. Paraffin blocks were stained with H and E and immunohistochemistry done for androgen receptor and Ki-67. The patients were also contacted and asked to come to hospital. Detailed history and clinical examination were done to assess the current status of the patient.

Statistical Analysis

Data was analysed using standard analytical techniques with SPSS version 16.0 for windows. The associations between study variables were analysed using Chi-square test and 'p' values less than 0.05 were considered significant. The main outcome parameters studied were recurrence (whether happened or not) and survival (alive or dead). The diagnostic efficacy parameters for prediction of poor outcome for tumour grade, AR positivity and grade + AR positivity were analysed.

RESULTS

Age of the patients ranged from 40-88 years with a mean age of 63.07 years. The maximum number of patients belonged to 60-69 years. Majority of the patients were males constituting 87% (n=40) of cases. Of the 46 cases, 33 patients (71.7%) were having low-grade urothelial carcinoma and 13 patients (28.3%) were having high-grade urothelial carcinoma. Only 3 cases (6.5%) were androgen receptor positive. All were males and 43 cases were androgen receptor negative (93.5%). 9 patients (19.6%) had recurrence, 32 patients had no recurrence and 5 patients (10.9%) died of the disease, all males. None among

the six female patients died. Out of 33 low-grade cases, only 1 case (3% of low-grade cases) was androgen receptor positive. Out of 13 high-grade cases, only 2 cases (15.4% of high-grade cases) were androgen receptor positive.

Out of 33 low-grade cases, 6 patients showed recurrence, 23 cases showed no recurrence and 4 patients died. Out of 13 high-grade cases, 3 patients showed recurrence and 9 patients showed no recurrence and one patient died.

Out of 3 androgen receptor positive cases, 1 patient (33.3%) died and 2 patients (66.7%) are alive. Out of 43 androgen receptor negative cases, 4 patients (9.3%) died, 8 patients showed recurrence and 31 patients showed no recurrence.

Of the total 46 cases, 19 cases were having Ki-67 positivity more than 5 percentage and 27 cases with less than 5 percentage. All the three androgen receptor positive cases (6.5% of total cases) were having Ki-67 positivity percentage more than 5. Out of 43 androgen negative cases (93.5% of total cases), 16 cases were having Ki-67 positivity more than 5% and 27 cases were having Ki-67 positivity less than 5% (Table 2).

All the five patients who died were males of age more than 40 years. Only one patient was androgen receptor positive and four patients were androgen receptor negative. Two patients were having Ki-67 count more than 5/100 cells and 3 patients were having Ki-67 count less than 5 per 100 cells. One patient died was having high-grade carcinoma and 4 patient died was having low-grade carcinoma (Table 3).

Out of 46 cases studied, 9 cases showed recurrence. Of the 9 recurred cases, 4 patients were of age less than 40 years and 5 patients were of age more than 40 years. 8 patients were males and 1 patient was female. Of the 9 cases with recurrence, one patient was with androgen receptor positivity and 8 patients were androgen receptor negative. Six patients showed Ki-67 count more than 5 per 100 cells and 3 patients showed Ki-67 count less than 5 per 100 cells. Of the 9 cases recurred, 3 cases were high grade and 6 cases were low grade. All the androgen receptor positive cases had high Ki-67 values (Table 4).

		Androgen Positivity			Recurrence			Mortality		
		Positive	Negative	Total	Yes	No	Total	Dead	Alive	Total
Male	No	3	37	40	8	27	35	5	35	40
	%	(7.5%)	(92.5%)	(100.0%)	(22.9%)	(77.1%)	(100.0%)	(12.5%)	(87.5%)	(100.0%)
Female	No	0	6	6	1	5	6	0	6	6
	%	(0%)	(100.0%)	(100.0%)	(16.7%)	(83.3%)	(100.0%)	0	100%	100%
Total	No	3	43	46	9	32	41	5	45	46
	%	6.5%	93.5%	100.0%	(22.0%)	(78.0%)	(100.0%)	10.9%	89.1%	100.0%

Table 1. Androgen Positivity, Recurrence of Tumour and Mortality According to Sex

		Ki-67 >5	Ki-76 <5	Total
AR+	No	3	0	3
	%	6.5%	0	6.5%
AR-	No	16	27	43
	%	34.8%	58.7%	93.5%
Total	No	19	27	46
	%	41.3%	58.7%	100.0%

Table 2. Androgen Receptor Positivity and Ki-67 Positivity

Parameter	Yes	No	P
Age <40 years	0 (0)	5 (17.9)	0.0716
Male sex	5 (12.5)	0 (0)	0.048
Androgen receptor positivity	1 (33.3)	4 (9.3)	0.2977
Ki-67 count >5/100 cells	2 (10.5)	3 (11.1)	0.667
High grade	1 (7.7)	4 (12.1)	0.5612

Table 3. Influence of Different Variables on Outcome No. (%) of those who Died of Disease

Parameter	Yes	No	p
Age <40 years	4 (23.5)	5 (26.3)	0.5776
Male sex	8 (25.8)	1 (20)	0.6331
Androgen receptor positivity	1 (100)	8 (22.9)	0.25
Ki-67 count >5/100 cells	6 (28.6)	3 (20.0)	0.4274
High grade	3 (33.3)	6 (22.2)	0.3984

Table 4. Influence of Different Variables on Outcome No. (%) of those who had Recurrence of Tumour

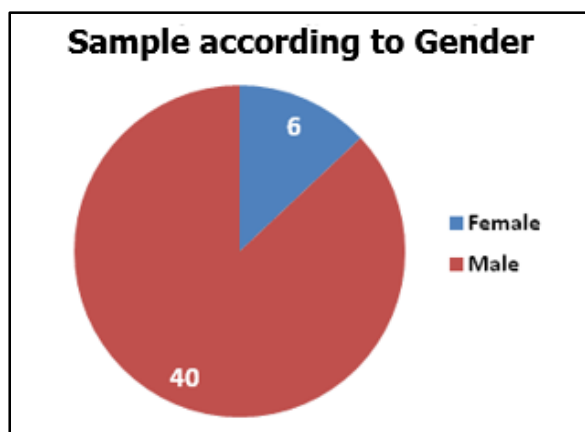


Figure 1. Sex Distribution

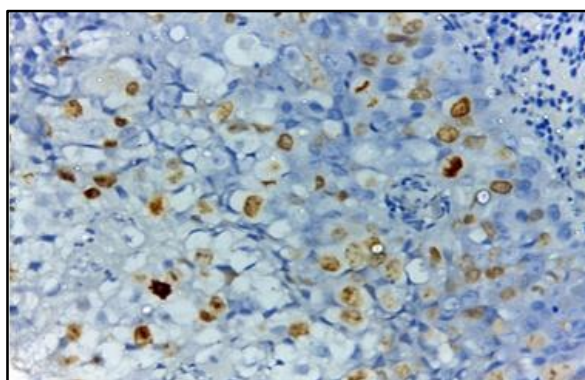


Figure 2. AR Positivity in Urothelial Carcinoma

DISCUSSION

Comparative studies have demonstrated that men are 3 to 4 times more likely to develop bladder cancer than women, environmental or lifestyle factors such as industrial chemicals and cigarette smoke have been blamed for the gender-specific differences in bladder cancer incidence and aggressiveness. However, even after controlling these carcinogenic factors, bladder cancer remains a predominant disease among men. Recent studies have provided data supporting the hypothesis that Androgen Receptor (AR) signaling plays an essential role in the development and progression of bladder cancer, which may explain some of the differences between male and female tumours.⁷

In a study conducted by Arshad Rahmani et al, it is reported that expression of androgen receptor was seen to be significantly higher in male in the age group of 50 years and above (p <0.05), AR expression was found to be associated significantly with the tumour grades, age and sex

suggesting that AR maybe used as prognostic marker in the treatment of urinary bladder carcinoma.⁶

In a recent and the largest study conducted by Mir C, Shariat SF et al involving 492 patients, only 13% of bladder tumours were found to show AR expression.⁸ In both studies, majority of the cases were high-grade carcinomas. Another study conducted by Miyamoto H, Yao JL, Chaux A et al showed that AR stained positively in 79 (42%) of 188 bladder tumours.⁹

According to the available data, AR expression in bladder cancer is controversial. Tuygun and colleagues¹⁰ reported a significant decrease in AR expression in higher grades and invasive tumours, which is consistent with the findings of Boorjian and colleagues¹¹ in contrast, Mir and colleagues⁸ in a study involving 472 patients showed that AR positivity was higher in muscle invasive tumours. In another study with 33 superficial bladder cancers, author reported that patients with high AR expression tend to have a high recurrence rate compared to patients with low AR expression. Birtle and colleagues¹² and Zhuhang and colleagues¹³ studied AR expression in high grade of the bladder and showed they mentioned that AR expression can be used as a diagnostic marker.

Our study aimed to determine the relation between Androgen Receptor (AR) positivity and grade of urothelial carcinoma and to determine the relation between AR positivity and grade individually and also in combination with the main outcome parameters namely, recurrence and survival in urothelial carcinomas. A total of 46 cases with histopathological diagnosis of urothelial carcinoma is included in the study. Out of the 46 cases, only three were androgen receptor positive (6.5%) and the remaining 93.5% were androgen receptor negative. This decreased AR positivity in our study maybe because large number of cases were low-grade carcinomas (71.7%).

Age and Sex

Age of the patients ranged from 40 to 88 years. The maximum number of patients belonged to male sex constituting 87% (n=40) of cases.

Grade and AR Receptor Positivity

33 patients were having low-grade carcinoma and the remaining 13 patients were having high-grade carcinoma. Out of 46 cases, only 3 cases showed AR positivity, of which two cases was high grade and one case was low grade. Out of 3 AR positive cases, one patient died, one patient showed recurrence and the other patients showed no recurrence.

Survival and Recurrence

Out of 46 cases, 9 patients showed recurrence, of which one patient was AR positive and the remaining 8 were AR negative at initial diagnosis. Of the 46 cases, 5 patients died, of which one patient who was AR positive and the remaining 4 were AR negative. Of the 5 patients died, one patient was high grade and 4 patients were having low-grade carcinoma.

Ki-67 Positivity and AR Positivity

Of the total 46 cases, 19 cases were having Ki-67 positivity more than 5 percentage and 27 cases with less than 5 percentage and all the three AR positive was having Ki-67 positivity more than 5 percentage, which was statistically significant (p value = 0.03).

In this study, we could make out statistically significant relation between AR positive cases and Ki-67 positivity more than 5% (p = 0.03).

In this study, we could not make out any statistically significant association between grade and AR positivity of the carcinoma. Also, we cannot make out any relation between AR positivity and grade on initial diagnosis with recurrence and survival.

CONCLUSION

Urothelial carcinoma occurs predominantly in males. In our study, we could not prove any association between AR positivity and the grade of the tumour or with recurrence or the survival of the patients. We had only 46 cases. It may be the reason for not getting any association between these parameters. Many earlier studies were made on AR to understand the mechanism of androgen and AR in the genesis and progression of bladder carcinoma, but still the exact mechanism is not well defined. So, further researches maybe needed to explore the role of androgens and AR positivity in urothelial carcinomas.

REFERENCES

- [1] Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol* 2000;164(5):1523-1525.
- [2] Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol* 2013;64(4):639-653.
- [3] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10-29.
- [4] Babjuk M, Oosterlinck W, Sylvester R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol* 2011;59(6):997-1008.
- [5] Shariat SF, Favaretto RL, Gupta A, S, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol* 2011;29(4):481-486.
- [6] Rahmani A, Alzohairy M, Mandal AK, et al. Expressional evaluation of androgen receptor in transitional cell carcinoma of urinary bladder patients. *British Journal of Medicine & Medical Research* 2011;1(4):233-238.
- [7] Hartge P, Harvey EB, Linehan WM, et al. Unexplained excess risk of bladder cancer in men. *Journal of the National Cancer Institute* 1990;82(20):1636-1640.
- [8] Mir C, Shariat SF, van der Kwast TH, et al. Loss of androgen receptor expression is not associated with pathological stage, grade, gender or outcome in bladder cancer: a large multi-institutional study. *BJU International* 2011;108(1):24-30.
- [9] Miyamoto H, Yang Z, Chen YT, et al. Promotion of bladder cancer development and progression by androgen receptor signals. *J Natl Cancer Inst* 2007;99(7):558-568.
- [10] Tuygun C, Kankaya D, Imamoglu A, et al. Sex-specific hormone receptors in urothelial carcinomas of the human urinary bladder: a comparative analysis of clinicopathological features and survival outcomes according to receptor expression. *Urologic Oncology* 2011;29(1):43-51.
- [11] Boorjian S, Ugras S, Mongan NP, et al. Androgen receptor expression is inversely correlated with pathologic tumor stage in bladder cancer. *Urology* 2004;64(2):383-388.
- [12] Birtle AJ, Freeman A, Munson P. The androgen receptor revisited in urothelial carcinoma. *Histopathology* 2004;45(1):98-99.
- [13] Zhuang YH, Blauer M, Tammela T, et al. Immunodetection of androgen receptor in human urinary bladder cancer. *Histopathology* 1997;30(6):556-562.