RESEARCH ARTICLE

Evaluation of GATA3 Gene Expression from Urothelial Carcinoma and the Genitourinary System: Its Correlation with Histopathological Parameters

Noor alhuda Sabah Hussain[1], Haider Jabur Kehiosh[1], Fatima Mutasher Swadi[2*]

[1]*Alhussain Teaching Hospital, Kerbala, Iraq*
[2]*College of Medicine University of Kerbala, Iraq*

Received: 11th Aug, 2024; Revised: 15th Jun, 2025; Accepted: 15th Jul, 2025; Available Online: 25th Sep, 2025

ABSTRACT

Objective: Evaluation of the GATA3 utility in differentiating urothelial carcinoma from other malignant tumors of the genitourinanry system such as prostatic adenocarcinoma, and renal cell carcinoma. And correlation between GATA3 expression with other different parameters such as grade, stage, necrosis, and mitosis.

Method: 70 cases of urothelial carcinoma, 10 cases of prostatic adenocarcinoma, and 10 cases of renal cell carcinoma of papillary and clear cell variants were selected at the period between (jan. 2017 and sep. 2020), with age range 34 to 88, with mean age 73 years, histopathologically evaluated, then stained with GATA3 antibody, and reevaluated with semi quantitative immunoreactive score, finally GATA3 correlated with tumor grade, stage, necrosis, and mitosis.

Results: In this study GATA3 expressed in 84.3% of urothelial carcinoma cases, Expression used to be considerably correlated with tumor grade; (p value = 0.001) and stage (p value = 0.003), but not with number of mitosis (p value = 0.2) or necrosis (p value = 0.7), None of the prostatic adenocarcinoma, or renal cell carcinoma express GATA3.

Conclusion: GATA3 could be considered as a necessary precise sensitive and highly specific marker to confirm urothelial origin. It is effective marker if used in the appropriate clinical concepts, GATA3 expression is an independent factor predicting cancer recurrence, so it could be used as a prognostic marker not only diagnostic marker, No significant association found in this study between GATA3 expression and presence or absence of necrosis, or the number of mitosis.

How to cite this article: Noor alhuda Sabah Hussain, Haider Jabur Kehiosh, Fatima Mutasher Swadi. Evaluation of GATA3 Gene Expression from Urothelial Carcinoma and the Genitourinary System: Its Correlation with Histopathological Parameters. International Journal of Drug Delivery Technology. 2025;15(3):1001-05. doi: 10.25258/ijddt.15.3.14

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Bladder cancer is the 11th most common cancer worldwide, and the 13th most common cause of death[1], i.e. it's responsible for 2.1% of cancer deaths worldwide[2], with male to female ratio of 3.5:1[3], about 90% of cases are 55 years and older[1]. Urothelial carcinoma comprises approximately 90% of all primary tumors of the bladder[4]. The diagnosis of urothelial carcinoma depends on microscopic evaluation of bladder biopsy, which is usually easily diagnosed, but in selected cases it's hard to decide the origin of malignant cells whether it's from bladder or other sites of the urogenital system based on microscopic evaluation only, several immunohistochemical markers used for this purpose.

Neoplastic urothelial cells express CK7, CK20, p63, and high-molecular-weight cytokeratin. GATA3 commonly shows nuclear staining in urothelial carcinoma. Different uroplakin antibodies have also been reported to show immunoreactivity in urothelial carcinoma, with uroplakin II may have more utility[4].

GATA3-binding protein, is a transcription factor belongs to GATA proteins family, those proteins recognize G-AT-A sequences and bind in the form of ([A/T] GATA[A/G]) leads to activate or repress those genes[5], It has 2 zinc fingers at the carboxyl terminus and belongs to a distinct family of tumor suppressor genes[6].

It was primarly identified asa T cell development regulators. GATA3 presents in normal tissues and regulate its normal development including hemopoietic, as T cells, and non-hemopoietic tissues, as the kidney, lens, sympathetic central nervous system, skin, thymus, luminal cells of mammary gland, adipose tissue, urothelium, parathyroid gland, endothelial cells, trophoblast, seminal vesicle epithelium, salivary glands and prostatic basal cells[7].

It has been recently used in histopathology as a marker for breast and urothelial carcinomas[8].and found to be downregulated in invasive bladder cancers[9].

In bladder, it was expressed in bladder cancer weaker than the normal urothelium, this suggested that decrease GATA3 expression may be necessary for tumor initiation or maintenance. Loss of GATA3 down-regulated the expression of tumor suppressors, such as UGT1A, PTEN, p53, and p21, and up-regulated that of oncogenic genes, such as c-myc, cyclin D1, cyclin D3, cyclin E, and FGFR3.The role of GATA3 in normal urothelial cell development has yet to be elucidated[10].

METHOD

Seventy cases of urothelial carcinoma, ten cases of prostatic adenocarcinoma, and ten cases of renal cell carcinoma (papillary and clear cell type) were collected from different hospitals and private laboratories in Karbalaa

**Author for Correspondence: fatimahisto78@gmail.com*

province, after ethical committee approval over a period between January 2017 and December 2019, cases were referred to Alhussain teaching hospital as a paraffin embedded blocks for histopathological evaluation, Ten cases of well differentiated breast carcinoma, normal salivary gland tissue also collected and proved by the microscopical examination were considered as positive control group, Negative control group were sections untreated with primary antibody (GATA3).

Review for all slides histopathologically, and confirmation of the diagnosis, pathological staging according to WHO 2016 staging system, grading as low grade and high grade, presence or absence necrosis, and number of mitosis was done for every case. 4 µm thickness taken from paraffin blocks for immunohistochemical application of anti GATA3 monoclonal rabbit IgG, 3 ml, pathnsitu.

Nuclear staining positivity assessed by the IRS (immunoreactive scoring) system[11].

RESULTS

Study Demographics and Pathological Characteristics

A total of 90 cases were included in the study: 70 cases of urothelial carcinoma, 10 cases of prostatic adenocarcinoma, and 10 cases of renal cell carcinoma.

Urothelial Carcinoma

The age range was 34 to 88 years, with a mean age of 73.5 years. Males constituted 75.7% and females 24.3% of the cases, resulting in a male-to-female ratio of approximately

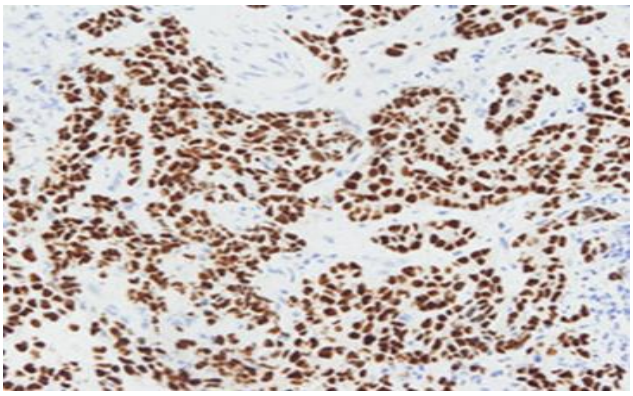

Figure 1: GATA3 expression in invasive ductal carcinoma of breast (control)

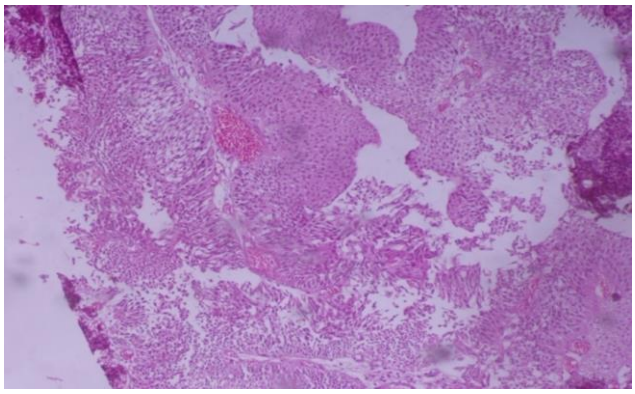

Figure 2: Papillary urothelial carcinoma (low grade) H & E

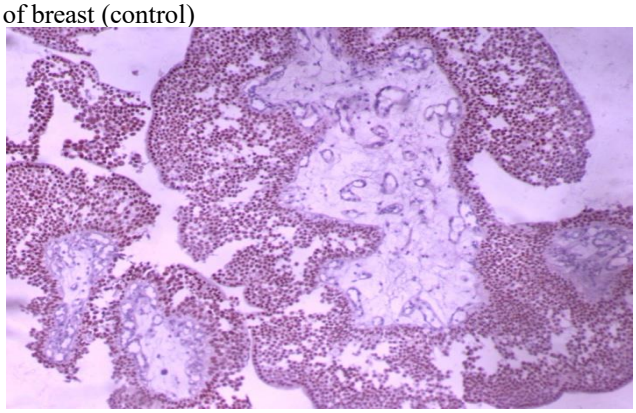

Figure 3: GATA3 expression in Low grade papillary urothelial carcinoma

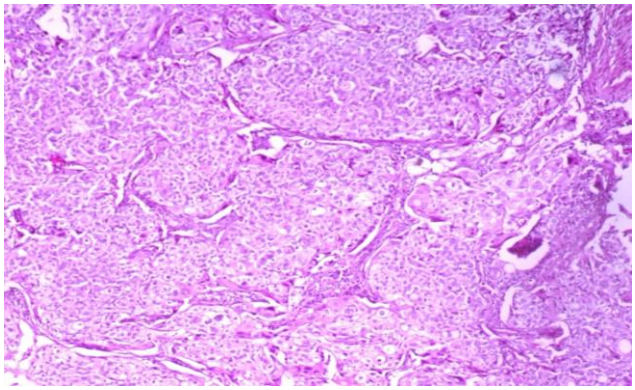

Figure 4: High grade papillary urothelial carcinoma H & E

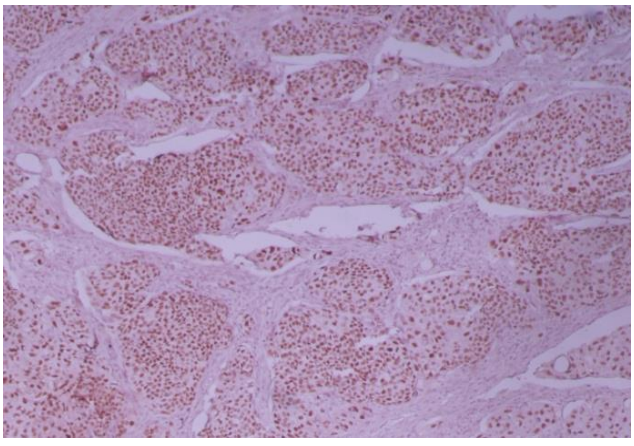

Figure 5: GATA3 expression in high grade urothelial carcinoma

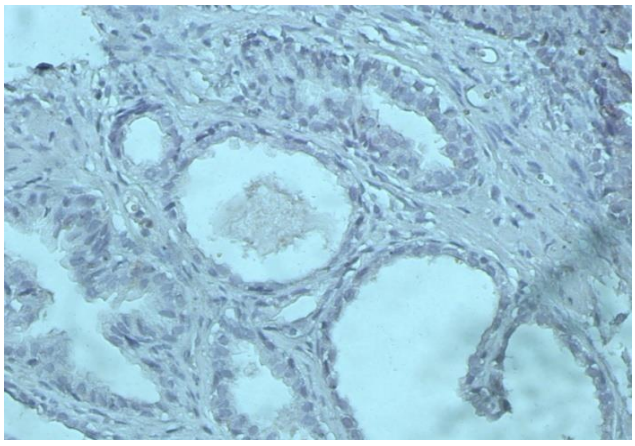

Figure 6: prostatic adenocarcinoma with negative GATA3

Table1: Immunoreactive score system

Percentage of positive cells	Intensity of staining	IRS score= multiplication of percentage and intensity
0 = no staining	0= no color reaction	0_1= negative
1= <10% of positive cells	1= mild color reaction	2_3= mild
2= 10%-50% of positive cells	2= moderate color reaction	4_8= moderate
3= 50-80% of positive cells	3= strong color reaction	9_12= strong
4= >80% of positive cells		

Statistical Analysis of all results were performed by the help of SPSS statistical package at level of significance alpha=0.05 to find (P value).

3:1. Non-invasive urothelial carcinoma (stages Ta and T1) accounted for 51.4% of the cases, while invasive carcinoma (stages T2, T3, and T4) comprised 48.6%. Histologically, 50% of the tumors were low grade and 50% were high grade.

Prostatic Adenocarcinoma

Patients ranged in age from 52 to 85 years, with a mean of 68.1 years. According to the Gleason grading system, the distribution was as follows: 10% each for grades 1, 2, and 3; 50% for grade 4; and 20% for grade 5.

Renal Cell Carcinoma

The age range was 28 to 70 years, with a mean age of 52.2 years. Males accounted for 60% and females for 40% of the cases, giving a male-to-female ratio of 1.5:1. According to the WHO/ISUP grading system for clear cell and papillary RCC, 20% were grade 1, 50% were grade 2, and 30% were grade 3.

Immunohistochemical Analysis of GATA3

GATA3 expression was evaluated by nuclear staining of malignant cells using the semiquantitative immunoreactive scoring system (IRS118, 119, 120), which considers both the percentage and intensity of staining. Positive GATA3 expression was recorded in 84.3% of cases. The positive cases were further categorized into four groups based on staining intensity and extent.

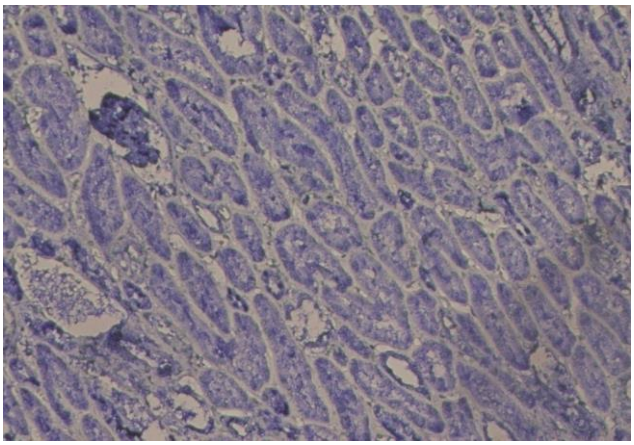

Figure 7: Papillery renal cell carcinoma with negative GATA3 expression

Table 2: Immunohistochemical expression of GATA3 in urothelial carcinoma

group	GATA3 expression	Number of patients	percentage
group 1	Negative	11	15.7%
Group 2	Weak	21	30%
Group 3	Moderate	19	27.1%
Group 4	strong	19	27.1%

Table 3: Clinicopathological parameters of urothelial carcinoma

Clinicopathological parameters		Urothelial carcinoma cases	
		number	percentage
age	65 years or less	39	55.7%
	More than 65 years	31	44.3%
gender	male	53	75.7%
	female	17	24.3%
stage	Ta	13	18.6%
	T1	23	32.9%
	T2	27	38.6%
	T3	2	2.9%
	T4	5	7.1%
Grade	Low grade	35	50%
	High grade	35	50%
mitosis	Less than 5/10HPF	38	54.3%
	5_10/10HPF	23	32.9%
	More than 10/10HPF	9	12.9%
necrosis	absent	56	80%
	present	14	20%

Expression of GATA3 protein in urothelial carcinoma in association with grade revealed that positive GATA3 reported 94.2% of low grade cases, and 74.2% of the high grade cases. There is significant correlation between GATA3 staining and tumor grade with P value (less than 0.05).

Expression of GATA3 in relation to stage revealed that with increased pathologic T stage, GATA3 staining decrease in intensity and percentage, significantly with stage 3 and 4, with all Ta cases were moderately to strongly positive, 95.6% of T_1 were positive, 74% of T_2 cases were positive, 50% of T_3 cases were positive, and 60% of T_4 cases were positive. significant correlation between GATA3 and tumor stage P value < 0.05. Correlation between GATA3 expression and number of mitoses despite the presence of correlation between GATA3 expression and number of mitosis, but P value is not significant (0.2) Regarding correlation between GATA3 reactivity and presence of necrosis, The correlation is not significant P value = 0.07.

All cases of prostatic adenocarcinoma, papillary renal cell carcinoma, and clear cell renal cell carcinoma were negative for GATA3.

DISCUSSION

Approximately 80% of urothelial carcinoma cases can be diagnosed using hematoxylin and eosin (H&E) staining alone. However, diagnosis can be challenging due to the tumor's wide range of histological patterns and its overlap with direct invasion or metastases from other genitourinary sites. Early and accurate diagnosis of urothelial carcinoma

is essential, as it requires aggressive treatment protocols that differ significantly from those used for metastatic tumors from other primary sites[6].

Immunohistochemistry (IHC) plays a critical role in differentiating urothelial carcinoma from metastatic malignancies. While several IHC markers are available for this purpose, many have limited sensitivity or specificity. For example, uroplakin III demonstrates high specificity but low sensitivity. Markers such as p63, S-100, and thrombomodulin exhibit high sensitivity but are not specific to urothelial origin.

GATA3, a relatively recent IHC marker, has shown promise when used alone or in combination with other markers. Reported positivity rates for GATA3 range from 67% to 90%, though the staining intensity and percentage may vary based on tumor grade, variant, and metastatic status[12]. GATA3 was first investigated for urothelial carcinoma by Higgins et al. in 2007[14].

Study Findings

In this study, 90 cases were analyzed, comprising 70 cases of urothelial carcinoma, 10 cases of prostatic adenocarcinoma, and 10 cases of renal cell carcinoma. GATA3 antibody was applied to all cases, revealing a sensitivity of 84.3% for urothelial carcinoma—comparable to previous studies[15,16].

A highly significant association was found between GATA3 staining intensity and tumor grade ($P < 0.001$). GATA3 positivity was observed in 94% of low-grade tumors versus 74% of high-grade tumors, aligning with prior findings[3,12].

A significant correlation was also observed between tumor stage and GATA3 expression ($P = 0.003$). Non-muscle-invasive urothelial carcinomas (Ta and T1) showed a 97% positivity rate, whereas muscle-invasive tumors (T2, T3, and T4) had a 70.5% positivity rate. Non-muscle-invasive tumors generally exhibited moderate to strong staining, while muscle-invasive tumors showed weaker to moderate staining patterns, echoing similar studies[3,12,17].

Recent studies have examined GATA3 as a prognostic factor, noting a decline in expression with increasing tumor grade or stage. Interestingly, some reports have also found strong GATA3 expression to be an independent marker of poor prognosis in male patients with muscle-invasive disease[18,19].

Regarding other histopathological features, no significant correlation was found between GATA3 expression and the mitotic count per 10 HPF ($P = 0.2$). This variability may be attributed to molecular subtypes of urothelial carcinoma, differences in mitotic count methodology, or lack of comparative studies.

Similarly, no significant association was observed between GATA3 expression and tumor necrosis ($P = 0.19$). Although necrosis is typically linked to higher tumor grade and stage[20], additional studies are needed to explore its potential correlation with GATA3 expression.

Notably, all cases of prostatic adenocarcinoma were negative for GATA3, reinforcing its role in differentiating urothelial carcinoma ($P < 0.001$). This finding is consistent with previous studies that support GATA3 as a specific marker for urothelial carcinoma over prostatic malignancies[3,7,15,21-24].

Furthermore, all renal cell carcinoma cases were GATA3-negative, which was also statistically significant ($P < 0.001$). Although limited, existing research supports GATA3's utility in distinguishing urothelial carcinoma from clear cell and papillary renal cell carcinomas[3,16,25].

Table 4: GATA3 correlation with histopathological parameters

Histopatho-logical parameter	GATA3 positive		GATA3 negative		P value
	No.	%	No.	%	
Tumor grade					
Low grade	33	94.2%	2	5.7%	P value < 0.05
High grade	26	74.2%	9	25.7%	
Tumor stage					
Stage Ta	13	100%	0	0%	
Stage T1	22	95.6%	1	9.1%	P value = 0.003
Stage T2	20	74%	7	63.6%	
Stage T3	1	50%	1	50%	
Stage T4	3	60%	2	18.2%	
Number of mitosis					
<5/10HPF	35	92.1%	3	7.9%	P value >0.05
5_10/10HPF	17	73.9%	6	26.1%	
>10/10HPF	7	77.7%	2	22.2%	
Necrosis					
Present	11	78.6%	3	21.4%	P value >0.05
absent	48	85.7%	8	14.2%	

Table 5: GATA3 expression in prostatic adenocarcinoma and renal cell carcinoma

Tumor	Positive		Negative		Total	P value
	No.	%	No.	%		
RCC	0	0%	10	100%	10	P value < 0.05 (0.01)
Prostatic adenocarcinoma	0	0%	10	100%	10	

CONCLUSION

GATA3 could be considered as a sensitive and highly specific marker to confirm urothelial origin. It is effective marker if used in the appropriate clinical concepts.

Strong association found between GATA3 and urothelial carcinoma histopathological parameters such as grade and stage, so it could be used as a prognostic marker not only diagnostic marker.

REFERENCES

1. Szymanska K, T Bosman, F, Hainaut P. Bladder Cancer: Pathology, Genetics, Diagnosis, and Treatment. elsevier. 2019;.
2. Rana C, Agarwal H, Babu S, Kumar M, Singhai A, Shankhwar S et al. Diagnostic utility of GATA3 immunohistochemical expression in urothelial carcinoma. Indian Journal of Pathology and Microbiology. 2019;62(2):244.
3. Mohammed K, Siddiqui M, Cohen C. GATA3 immunohistochemical expression in invasive urothelial

carcinoma. Urologic Oncology: Seminars and Original Investigations. 2016;34(10):432.e9-432.e13.
4. Leivo M, Elson P, Tacha D, Delahunt B, Hansel D. A combination of p40, GATA-3 and uroplakin II shows utility in the diagnosis and prognosis of muscle-invasive urothelial carcinoma. Pathology. 2016;48(6):543-549.
5. Zhou M, Magi_Galluzi C. Genitourinary Pathology. 2nd ed. 2015. Pages 181 to 247.
6. Gakis G, Todenhofer T, Renninger M, Schilling D, Sievert KD, Schwentner C, Stenzl A. Development of a new outcome prediction model in carcinoma invading the bladder based on preoperative serum C-reactive protein and standard pathological risk factors: the TNR-C score. BJU Int. 2011;108(11):1800–5.
7. Bladder cancer and upper tract cancer. Scardino PT, Lineham WM, Zelefsky MJ & Vogelzang NJ (eds.). (2011). Comprehensive Textbook of Genitourinary Oncology. (4th Edition). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. PartII:Chapter15:287- 504.
8. Cheng L, Weaver AL, Leibovich BC, et al. Predicting the survival of bladder carcinoma patients treated with radical cystectomy. Cancer. 2000;88:2326-2332.
9. Gakis G, Todenhofer T, Renninger M, Schilling D, Sievert KD, Schwentner C, Stenzl A. Development of a new outcome prediction model in carcinoma invading the bladder based on preoperative serum C-reactive protein and standard pathological risk factors: the TNR-C score. BJU Int. 2011;108(11):1800–5.
10. Hoffmann AC, Wild P, Leicht C et al (2010) MDR1 and ERCC1 expression predict outcome of patients with locally advanced bladder cancer receiving adjuvant chemotherapy. Neoplasia 12:628–636.
11. Miyamoto H, Izumi K, Yao JL, et al. GATA binding protein 3 is down-regulated in bladder cancer yet strong expression is an independent predictor of poor prognosis in invasive tumor. Hum Pathol. 2012;43:2033–2040.
12. Rosai J, Ackerman L, Goldblum J, Lamps L, McKenney J, Myers J. Rosai and Ackerman's surgical pathology. Philadelphia: Elsevier; 2018. Pages 1073 to 1079.
13. Soloway MS, Lopez AE, Patel J, Lu Y. Results of radical cystectomy for transitional cell carcinoma of the bladder and the effect of chemotherapy. Cancer 1994;73:1926–31.
14. Van Esch H, Groenen P, Nesbit M, Schuffenhauer S, Lichtner P, Vanderlinden G et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature. 2000;406(6794):419-422.
15. McCleskey BC, Penedo TL, Zhang K, et al. GATA3 Expression in Advanced Breast Cancer Prognostic Value and Organ-Specific Relapse. Am J Clin Pathol. 2015;144:756-763.
16. Yi Li, Hitoshi Ishiguro,Takashi Kawahara, et al. GATA3 in the urinary bladder: suppression of neoplastic transformation and down-regulation by androgens. Am J Cancer Res. 2014; 4(5): 461–473.
17. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66:7-30.
18. Bostwick DG, Burke HB, Djakiew D, et al. Hum Prostate cancer risk factors. Cancer. 2004;101:2371-2490.
19. Inoue S, Mizushima T, Fujita K, Meliti A, Ide H, Yamaguchi S et al. GATA3 immunohistochemistry in urothelial carcinoma of the upper urinary tract as a urothelial marker and a prognosticator. Human Pathology. 2017;64:83-90.
20. Peter A. Humphrey, Holger Moch, Antonio L. Cubilla, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. EUROPEAN UROLOGY. 2016; 70:106-119
21. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol. 2014;38(1):13-22.
22. Skinner DG, Colvin RB, Vermillion CD, et al. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. Cancer. 1971;28(5):1165-1177.
23. Brunelli M, Gobbo S, Menestrina F, et al. Core biopsies of renal tumors: accuracy for histopatholigical evaluation. Lab Invest. 2009;89(suppl 1):161A.
24. Remmele W, Stegner HE: Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathol 1987, 8:138–140
25. Krajewska M, Krajewski S, Epstein JI, Shabaik A, Sauvageot J, Song K, Kitada S, Reed JC: Immunohistochemical analysis of bcl-2, bax, bcl-X, and mcl-1 expression in prostate cancers. Am J Pathol 1996, 148:1567–1576.