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Original Article

TROP2 and SOX-10 expression in the differential diagnosis of bladder tumors

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Abstract

Aim: TROP2 is a member of the calcium signal converting gene family, which is highly expressed in various cancers. SOX10 is the nuclear transcription factor associated with the formation and development of various cancers. We investigated the importance of TROP2 and SOX10 in the differential diagnosis of tumoral lesions of the bladder.

Materials and Methods: TROP2 and SOX10 expressions were evaluated by immunohistochemical method in 150 tumoral and 20 non-tumoral bladder tissues.

Results: Strong staining with TROP2 was frequently seen in cases of papillary urothelial neoplasm with low malignant potential. There was no significant difference in the intensity of staining between the nontumoral group and the carcinoma groups, and between noninvasive carcinomas and invasive carcinomas.

Conclusion: Although strong staining with TROP2 indicates tumoral development, widespread staining does not show this. Expression loss in TROP2 is observed in muscle invasive carcinomas. Strong and widespread (≥ 50%) TROP2 staining indicates papillary urothelial neoplasm with low malignant potential. Evaluation of this finding together with histomorphological findings may help to make an accurate diagnosis.

Keywords: Bladder cancer; immunohistochemistry; SOX10; TROP2

INTRODUCTION

Although urothelial carcinoma (UC) may occur in any region of the urinary tract, most commonly it affects the bladder. In the United States, it is the type of cancer that is seen as the 4th most common cancer in males and 12th in females. Bladder cancer is often diagnosed in patients older than 50 years of age (1). Hematuria is the most commonly seen symptom (1,2). Approximately 90% of bladder cancers are urothelial carcinomas derived from the urothelial epithelium (2-6).

Noninvasive urothelial carcinomas constitute most of the primary bladder tumors and are structurally classified as flat and papillary lesions (7). 75% of invasive carcinomas are non-muscle invasive bladder cancers and 25% of them are muscle invasive bladder cancers (2,4,8).

Superficial bladder cancers may be confined in the mucosa, invasive to the lamina propria, or carcinoma in situ. The involvement of muscularis propria is considered as advanced cancer (3). In the treatment of UCs, the grade and stage of the tumor are important. While progression is less common in low grade tumors, progression and recurrence are more common in high grade tumors. While patients with low grade tumors are followed up clinically, in patients with high grade tumors, Bacillus Calmette-Guérin (BCG) or intravesical chemotherapeutic agents, and cystectomy is frequently performed in tumors that invade muscularis propria (1,2,4).

Trophoblast antigen 2 (TROP2) is a transmembrane glycoprotein consisting of 323 amino acids localized in the chromosome 1p32 gene region. TROP2 is a member of the tumor-associated calcium signal transducer gene family. It was first discovered in human trophoblasts and choriocarcinoma cell lines (9). There are extracellular and intracellular fragments in the trophoblasts in the placenta and on many cell surfaces (6, 9-11). The fact that overexpression of TROP2 seen in chorionic trophoblastic cells in areas where the placenta is implanted is present also in epithelial tumors also suggests that this glycoprotein may play a role in invasion and metastasis of tumor cells (8-11). TROP2 has been shown to be overexpressed in oral squamous cell cancer (9), breast cancer (12), stomach cancer (10), ovarian cancer (11), thyroid tumors (13-15), lung cancer (16,17) and nasopharyngeal cancers (18).

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Unlike these tumors, TROP2 shows low or no expression in normal tissues (9). TROP2 has been reported to show significantly more expression in bladder tumors than in normal tissues (6).

SOX10 (SRY-associated HMG-box 10) is a nuclear transcription factor that plays an important role in schwann cells and melanocytic cell differentiation and regulates the Wnt / β catenin signal pathway in various developmental processes (5,19-23). SOX10 is associated with the formation and development of salivary gland tumors, breast, nasopharyngeal, ovarian and prostate cancers. Overexpression of SOX10 acts as an oncogene by activating the Wnt / β catenin signal pathway in hepatocellular carcinoma, and acts as a tumor suppressor by inhibiting the Wnt / β catenin signal pathway in the digestive system cancers (5,19).

Grading and staging bladder cancers should be correctly is vital in terms of treatment to be applied to the patient. Because the progression and recurrence of the disease varies accordingly. It is also important for determining the follow-up of the disease (1-4,7). In grading papillary carcinomas; nuclear atypia, mitosis, loss of polarization and papillary structures are examined. Due to the subjective nature of these criteria, it causes different interpretation among the pathologists.

SOX10 and TROP2 are rarely or never seen in normal tissues. Studies have shown that SOX10 and TROP2 are associated with tumor differentiation and tumor progression. Therefore, in our study, we investigated the importance of SOX10 and TROP2 in the differential diagnosis of tumoral lesions of the bladder.

MATERIALS and METHODS

Patient Characteristics

Bladder Transurethral resection (TUR) specimens which were diagnosed as tumor (150 patients) and non-tumor lesions (20 patients) between the years of 2010 and 2018 in Selcuk University Faculty of Medicine, Department of Medical Pathology were evaluated.

After the approval of the Ethical Committee 05.12.2018 dated and 2018/418 numbered from the Ethical Committee of Non-Interventional Clinical Researches, Faculty of Medicine, Selcuk University, slides stained with Hematoxylin-Eosin (HE) were reevaluated by two pathologists (NSU and IH) according to the classification in the 2016 edition book of the World Health Organization. Twentynon-tumor / chronic inflammation (CI), 20 papillary urothelial neoplasms of low malignant potential (PUNLMP),

Thirty fivenon-invasive low grade papillary urothelial carcinoma (NILGPUC), 20 non-invasive high grade papillary urothelial carcinoma (NIHGPUC), 15 lamina propria invasive low grade papillary urothelial carcinoma (LPILGPUC), 20 urothelial carcinomas in situ (UCIS), 20 lamina propria invasive high grade urothelial carcinoma (LPIHGUC) and 20 muscle invasive high grade urothelial carcinoma (MIHGUC) were selected.

Immunohistochemistry

Sections of 4μm thickness obtained from selected paraffin blocks were deparaffinized and hydrated. Then, in the automatic staining system of the Dako Omnis mark, after antigen recovery (retrieval) stage with 0.01 M Sodium Citrate buffer (pH 6.0) and heat stimulation, endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 15 minutes. SOX10 (monoclonal antibody, 1: 100 dilution, clone SP275, Abcam, USA) and TROP2 (monoclonal antibody, 1:50 dilution, clone B-9, Santa Cruz Biotechnology, USA) antibodies were incubated. After secondary antibody staining, reacted with diaminobenzidine (DAB) as chromogen for 3 minutes and then nuclei were counterstained using hematoxylin.

Immuno-Activity Evaluation

Slides stained with TROP2 and SOX10 were scored according to the staining intensity and positive staining percentage. According to the staining percentage; The score was evaluated as 0 (no staining), score 1 (staining <10%), score 2 (staining 10-50%), score 3 (staining 50%). Staining intensity was evaluated as score 0 (no staining), score 1 (light staining), score 2 (moderate staining), score 3 (significant staining) (18). Both scores will be evaluated separately between the groups.

Statistical Analysis

The intensity and percentage of the expression of antibodies according to histomorphological differences were analysed with the SPSS 21 (SPSS Inc., Chicago, IL) statistical program. Whether the data fit the normal distribution was evaluated with the Kolmogorov Smirnov test. Normality was tested with data transformation processes to data that were found to not conform to the normal distribution. It was observed that the data did not conform to the normal distribution. The Mann Whitney U test was used for the comparison of the two groups, and the Kruskal Wallis Test was used for the comparison of multiple groups. In the Kruskal Wallis Test, the Kruskal Wallis Dunn Test was used for in-group paired comparisons. $P < 0.05$ values were considered to be statistically significant.

RESULTS

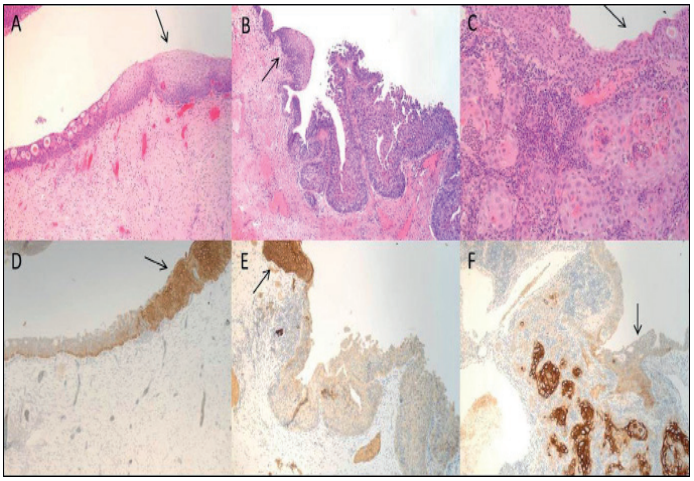
The diagnoses of a total of 170 patients with a mean age of 66 and the mean age according to these diagnoses are given in Table 1. Ninety-fivetumors (63.3%) were diagnosed as non-invasive tumors and fifty-five (36.7%) were diagnosed as invasive carcinoma. It was observed that the mean age of non-tumoral and tumoral cases ranged from 62 to 70 years (Table 1). Different staining patterns with TROP2 were observed in terms of staining intensity and staining percentage. In terms of staining intensity, low staining was observed in 113 cases, moderate staining in 25 cases and strong staining in 32 cases and low staining in 90% of CI patients, moderate staining in 10% of them. In terms of staining percentage, 4 cases was score 1, 19 cases was score 2 and 147 cases was score 3. Strong and score 3 staining was observed in squamous metaplasia areas and carcinoma foci showing

squamous differentiation in terms of staining intensity and percentage (Figure 1). In terms of staining intensity, 4 (20%) of PUNLMP cases were weak, 4 (20%) were moderate and 12 (60%) were strong, and in terms of percentage of staining, all of them were score 3 stained (Figure 2).

Table 1. Diagnoses and mean age of cases

	n	(%)	Diagnosis	Mean Age	n	(%)
	-	-	CI	62	20	11.8
			PUNLMP	64	20	11.8
			NILGPUC	64	35	20.6
Non-invasive	95	63.3	NIHGPUC	70	20	11.8
			UCIS	65	20	11.8
			LPILGPUC	69	15	8.8
Invasive	55	36.7	LPIHGUC	68	20	11.8
			MIHGUC	67	20	11.8
Total	150	100.0	Total		170	100.0

CI: Chronic Inflammation, PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential, NILGPUC: Non Invasive Low Grade Papillary Urothelial Carcinoma, NIHGPUC: Non Invasive High Grade Papillary Urothelial Carcinoma, UCIS: Urothelial Carcinoma In Situ, LPILGPUC: Lamina Propria Invasive Low Grade Papillary Urothelial Carcinoma, LPIHGUC: Lamina Propria Invasive High Grade Urothelial Carcinoma, MIHGUC: Muscle Invasive High Grade Urothelial Carcinoma



A: Normal Urothelial epithelium and squamous metaplasia (arrow), (Hematoxylin-eosin stain, original magnification, ×100); B: Urothelial carcinoma in situ and squamous metaplasia (arrow), (Hematoxylin-eosin stain, original magnification, ×100); C: Urothelial carcinoma with squamous differentiation and normal urothelial epithelium (arrow), (Hematoxylin-eosin stain, original magnification, ×200); D: Staining intensity of TROP2; normal urothelial epithelium score 1 staining and squamous metaplasia score 3 staining (arrow), (TROP2, original magnification, ×100); E: Staining intensity of TROP2; urothelial carcinoma in situ score 1 staining and squamous metaplasia score 3 staining (arrow), (TROP2, original magnification, ×100); F: Staining intensity of TROP2; urothelial carcinoma with squamous differentiation score 3 staining and normal urothelial epithelium score 1 staining (arrow), (TROP2; original magnification, ×100)

Figure 1. Hematoxylin-eosin and TROP2 staining

Table 2. Staining intensity of TROP2 antibody and p value

Diagnosis	Score 1		Score 2		Score 3		Total		X^2	P*
	n	%	n	%	n	%	n	%		
CI	18	90	2	10	0	0	20	11.76		
PUNLMP	4	20	4	20	12	60	20	11.76		
NILGPUC	23	65.5	4	11.5	8	23	35	20.6		
NIHGPUC	14	70	2	10	4	20	20	11.76		
UCIS	16	80	3	15	1	5	20	11.76	33.421	<0.001
LPILGPUC	12	81	2	13	1	6	15	8.84		
LPIHGUC	11	55	4	20	5	25	20	11.76		
MIHGUC	15	75	4	20	1	5	20	11.76		
Total	113	66	25	14	32	20	170	100		

*Kruskal Wallis Test
CI: Chronic Inflammation, PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential, NILGPUC: Non Invasive Low Grade Papillary Urothelial Carcinoma, NIHGPUC: Non Invasive High Grade Papillary Urothelial Carcinoma, UCIS: Urothelial Carcinoma In Situ, LPILGPUC: Lamina Propria Invasive Low Grade Papillary Urothelial Carcinoma, LPIHGUC: Lamina Propria Invasive High Grade Urothelial Carcinoma, MIHGUC: Muscle Invasive High Grade Urothelial Carcinoma

According to the data obtained on the intensity of TROP2 staining (Table 2,3);

a- It was observed that there was a significant difference between the groups with the Kruskal Wallis test (p = <0.001)

b- Low or moderate staining does not show tumoral development, whereas strong staining indicates tumoral development.

c- Strong staining is frequently seen in PUNLMP cases.

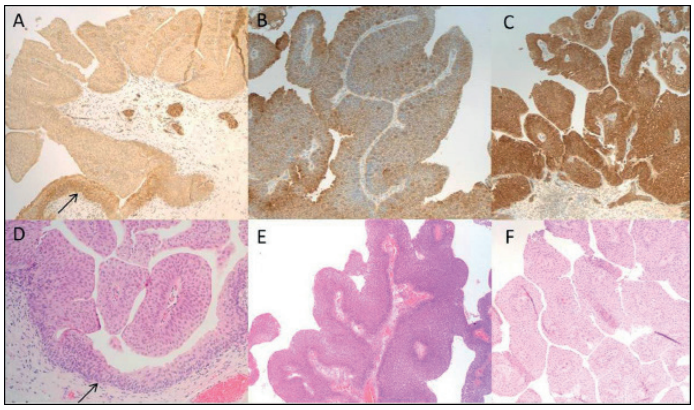
d- Tumors are always stained.

e- There are statistically significant differences between

PUNLMP group and CI, NILGPUC, LPILGPUC, NIHGPUC, UCI, LPIHGUC and MIHGUC groups (p=<0.001, 0.001, <0.001, 0.002, <0.001, 0.014, <0.001 respectively,)

f- There was no significant difference between CI and carcinomas (non-invasive and invasive) groups (p= 0.775) and non-invasive (NILGPUC, NIHGPUC, UCI) carcinomas and invasive (LPILGPUC, LPIHGUC, MIHGUC) carcinoma groups (p=0.208).

g- While in 25% of patients who have non-muscle invasive high grade invasive carcinomas show strong staining, this rate decreases to 5% in MIHGUC and this indicates loss of expression in muscle invasive tumors.



A- Score 1 staining in neoplastic epithelium with TROP2, Score 2 staining in normal urothelial epithelium (arrow) with (TROP2, original magnification, ×100); B- Score 2 staining in neoplastic epithelium with TROP2, (TROP2, original magnification, ×100); C- Score 3 staining in neoplastic epithelium with TROP2, (TROP2, original magnification, ×100) D- Neoplastic epithelium and normal urothelial epithelium (arrow), (Hematoxylin-eosin stain, original magnification, ×100); E- Tumor tissue (Hematoxylin-eosin stain, original magnification, ×200); F- Tumor tissue (Hematoxylin-eosin stain, original magnification, ×100)

Figure 2. A-F: Hematoxylin-eosin and TROP2 staining in papillary urothelial neoplasm of low malignant potential

Table 3. Comparison papillary urothelial neoplasm of low malignant potential group and other groups in terms of intensity of TROP2 expressions

	N	Mean Rank	Sum of Ranks	P value
PUNLMP	20	28.20	564.00	<0.001
CI	20	12.80	256.00	
PUNLMP	20	36.60	732.00	0.001
NILGPUC	35	23.09	808.00	
PUNLMP	20	23.00	460.00	<0.001
LPILGPUC	15	11.33	170.00	
PUNLMP	20	25.70	514.00	0.002
NIHGPUC	20	15.30	306.00	
PUNLMP	20	27.30	546.00	<0.001
UCIS	20	13.70	274.00	
PUNLMP	20	24.70	494.00	0.014
LPIHGUC	20	16.30	326.00	
PUNLMP	20	2710	542.00	<0.001
MIHGUC	20	13.90	278.00	

CI: Chronic Inflammation, PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential, NILGPUC: Non Invasive Low Grade Papillary Urothelial Carcinoma, NIHGPUC: Non Invasive High Grade Papillary Urothelial Carcinoma, UCIS: Urothelial Carcinoma In Situ, LPILGPUC: Lamina Propria Invasive Low Grade Papillary Urothelial Carcinoma, LPIHGUC: Lamina Propria Invasive High Grade Urothelial Carcinoma, MIHGUC: Muscle Invasive High Grade Urothelial Carcinoma

Table 4. Staining percentage of TROP2 antibody and p value

Diagnosis	Score 1		Score 2		Score 3		Total		X^2	P*
	n	%	n	%	n	%	n	%		
CI	0	0	4	20	16	80	20	11.76	9.125	0.244
PUNLMP	0	0	0	0	20	100	20	11.76		
NILGPUC	3	9	3	9	29	82	35	20.6		
NIHGPUC	0	0	3	15	17	85	20	11.76		
UCIS	0	0	1	5	19	95	20	11.76		
LPILGPUC	0	0	2	13	13	87	15	8.84		
LPIHGUC	0	0	3	15	17	85	20	11.76		
MPIHGUC	1	5	3	15	16	80	20	11.76		
Total	4	2	19	11	147	87	170	100		

***Kruskal Wallis Test**
CI: Chronic Inflammation, PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential, NILGPUC: Non Invasive Low Grade Papillary Urothelial Carcinoma, NIHGPUC: Non Invasive High Grade Papillary Urothelial Carcinoma, UCIS: Urothelial Carcinoma In Situ, LPILGPUC: Lamina Propria Invasive Low Grade Papillary Urothelial Carcinoma, LPIHGUC: Lamina Propria Invasive High Grade Urothelial Carcinoma, MIHGUC: Muscle Invasive High Grade Urothelial Carcinoma

According to the data obtained on the percentage of TROP2 staining (Table 4);

a- It was observed that there was no significant difference between the groups with the Kruskal Wallis test (p =0,244)

b- Staining was observed in the CI group and tumor groups, in half or often more than half of the tissue. Therefore, this situation does not indicate tumoral development.

c- There was no significant staining difference between non-invasive and invasive carcinoma groups (p=0.605), low grade and high grade carcinoma groups (p=0.960), MIHGUC and non-invasive carcinoma groups (p=0.147).

It was observed that there was no normal distribution between the groups with the Kolmogorov-Smirnov test. In pairwise comparisons of the groups, it was seen that there were statistically significant results between PUNLMP and other groups in terms of staining intensity with the Mann Whitney-U test (Table 3).

Malign Melanoma case was used as control block for SOX10 antibody. Nuclear staining was seen in our control case. Although Yin et al. (5) detected SOX10 staining in bladder tumors, no staining was observed in our tumoral and non-tumoral bladder groups.

DISCUSSION

TUR is performed in the diagnosis and staging of all superficial and invasive bladder cancers, treatment of superficial bladder cancer and sometimes palliative advanced stage bladder cancer treatments. 85% of bladder cancer cases are superficial and 15% are invasive tumors (3). Muscle invasive UCs are 25% of invasive carcinomas and non-muscle invasive UCs are 75% of them (4). Diagnostic difficulties are generally not encountered in invasive UCs. However, there may be diagnostic difficulties due to the variety of non-invasive urothelial neoplasms and the classification based on subjective properties (24). Architectural and cytological changes in bladder neoplasms are associated with clinical behavior (1). In high grade tumors and large tumor diameters, recurrence is common and failure to completely remove the tumor after the first TUR may result in relapse or progression (3). Diagnostic differences among pathologists can be seen more frequently in superficial tumors that make up the majority of bladder cancers. Sometimes it can be difficult to distinguish between PUNLMP and NILGPUC histomorphologically. In addition, difficulties may be experienced in distinguishing NILGPUC and NIHGPUC histomorphologically. Making this distinction correctly is important in terms of recurrence and progression of the disease sometimes it can be difficult to distinguish between PUNLMP and NILGPUC, NILGPUC and NIHGPUC. Making this distinction correctly is important for the relapse and progression of the disease. Although there are differences in molecular between low grade non-invasive carcinomas and high grade invasive carcinomas, using these tests for diagnosis leads to increased costs (1). In some high-grade tumors, p53 may be positive immunohistochemically. However, since it does not stain the majority of high-grade tumors, it cannot always be used in differential diagnosis. There is no very safe antibody to be used to distinguish low-grade tumors from high-grade tumors.We observed that there was common staining in most of the cases with TROP2 and there was no statistically significant difference between the groups, but there was a difference in terms of staining intensity between PUNLMP and NILGPUC cases, so we had difficulty in differential diagnosis. Strong staining was observed in most PUNLMP cases (60%) and low staining was observed in most of the NILGPUC cases (65.5%). This difference was statistically significant. (p=0,001)

There was no significant difference in the intensity of staining between CI and carcinoma (noninvasive and invasive) groups, non-invasive (NILGPUC, NIHGPUC, UCI) carcinomas and invasive (LPILGPUC, LPIHGUC, MIHGUC) carcinoma groups. While in 25% of patients who have non-muscle invasive high grade invasive carcinomas show strong staining, this rate decreases to 5% in MIHGUC and this indicates loss of expression in muscle invasive tumors. There was no significant staining difference in staining percentage between non-invasive and invasive carcinoma groups, low grade and high grade carcinoma groups, and MIHGUC and non-muscle invasive invasive carcinomas.

TROP2 has been shown to be overexpressed in many types of cancer. TROP2 has been proven to trigger oncogenic role in tumor formation and cell proliferation (8). It has also been reported that there are differences in expression between normal tissue and tumor tissue. It has been stated that there is a significantly higher expression of TROP2 in oral squamous cell cancers compared to normal epithelium, and there is a relationship between this expression and tumor differentiation, lymph node metastasis, tumor stage, perineural invasion and lymphovascular invasion (9). It has been shown that compared with normal mucosa TROP-2 levels were higher in also bladder cancers (6). In our study, there was no significant difference in staining intensity between non-tumoral bladder samples and tumoral bladder samples. It has been determined that TROP2 increases the oncogenic activity of bladder cancer cells, and by suppressing its expression, proliferation in tumor cells decreases and apoptosis increases (8).

We also observed that strong and common staining of TROP2, especially in squamous metaplasia areas and urothelial carcinomas showing squamous differentiation. Basing on this, it can be said that TROP2 can be used as a squamous differentiation or epidermoid carcinoma marker such as p40, p63, CK5/6 and HMWCK.

Wu et al suggest that TROP2 is correlated with histology grade, lymph node metastasis and TNM stage and predicts worse clinical outcomes. Moreover, our data have demonstrated that TROP2 overexpression promotes lung cell adenocarcinoma, cell proliferation, migration, invasion, and inhibits cell apoptosis. Therefore, these results support that TROP2 may serve as an oncogene in lung adenocarcinoma (11).

It has been reported that high TROP2 expression is associated with poor prognosis in lung cancers and higher overall mortality in lung adenocarcinomas (16). It has been emphasized that high TROP2 and Amphiregulin expression in stomach cancers is associated with poor prognosis and may be considered as an independent prognostic cobiomarker (10). It has been reported that TROP-2 is over-expressed in solid tumors. It has also been emphasized that it can be an ideal target for therapeutic development since it is attached to the cell membrane with an extracellular domain (25). However, in our study, the absence of distinctly different expressions in normal and tumor tissues, and the existence of TROP2 expression in non-tumor areas suggest that it is not an ideal therapeutic target. Although many studies emphasized that TROP2 expression is associated with tumor invasion, progression, and metastasis, we found that increased degree of the tumor did not significantly increase TROP2 expression in our study. We found that most of the invasive high grade tumors had weak staining in terms of staining intensity, which was not statistically significant. Although Yin et al reported that SOX10 was stained in 74.4% of bladder cancers and 32.6% of normal tissue samples (5), we did not see any staining with SOX10 in our study.

CONCLUSION

As a result;

a- Different staining patterns are seen in bladder tumors with TROP2,

b- Expression in PUNLMP cases show statistically significant differences with CI, NILGPUC, LPILGPUC, NIHGPUC, UCI, LPIHGUC and MIHGUC groups.

c- Since strong and common (≥ 50%) TROP2 staining indicates PUNLMP, evaluation of this finding together with histomorphological findings may help to get an accurate diagnosis,

d- It can be used as a squamous differentiation or epidermoid carcinoma marker such as p40, p63, CK5/6 and HMWCK, which are strongly and commonly stained in urothelial carcinomas showing squamous metaplasia and squamous differentiation.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: Selcuk University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee decision dated 05.12.2018 and numbered 2018/418.

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