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Original Article

Immunhistochemical expression of GLUT1 is associated with low grade and low stage of urinary bladder cancer

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Abstract: Many studies described glucose transporter 1 (GLUT1) as a fundamental player in cancer metabolism, which can be employed as a prognostic biomarker that may help in new treatment strategy development. This study will describe the pattern of GLUT1 expression in urinary bladder cancer and try to associate it with tumor clinicopathologic factors. Standard immunohistochemistry (IHC) staining protocol was utilized to identify the location and expression pattern of GLUT1 in a panel of 128 urinary bladder carcinoma compared to 24 normal tissues using tissue microarrays. GLUT1 expression was found up-regulated significantly in cancer cases, and it was found in 111 (86.7%) urinary bladder cancers compared to 4 (16.6%) of control cases ($P < 0.05$). Positive GLUT1 immunohistochemical staining was significantly correlated with low grade, low stage, and non-muscularis propria invasive urinary bladder cancer cases ($P < 0.05$). Log-rank test and Kaplan Meier survival curves displayed significant poor survival in stage III and stage IV patients ($P < 0.05$); mean survival is lowest at 29.924 months in stage IV patients. Similarly, significantly better survival is observed in low-grade tumors ($P < 0.05$). Urinary bladder cancer showed increased GLUT1 expression compared to a control group. IHC staining of GLUT1 can be a supportive tool in predicting prognostic and survival estimates of urinary bladder tumors with specific clinical and morphologic characteristics.

Keywords: GLUT1, immunohistochemistry, urinary bladder cancer

Introduction

Urinary bladder cancer is an important cause of cancer death around the world [1]. Considerable recurrence frequencies of this cancer and the possibility to proceed to a destructive, muscle-invasive and metastatic tumor, made it a huge challenge for physicians [2, 3]. There is a great necessity for better diagnostic markers and chemotherapeutic agents to facilitate clinical tasks for effective treatment of urinary bladder cancer.

Neoplastic cells show higher glucose metabolism in comparison with normal tissue [4]. The resultant growth in glucose demand indicates a need for a consistent rise in glucose transportation through the cellular membranes. Also, because of the need for energy to serve unrestrained proliferation, neoplastic cells frequently expresses glucose transporters which would not be expressed in cells in usual circumstances [5].

The glucose transporters (GLUTs) are expressed in the membranes of almost all types of cells [6]; Most of the 14 GLUTs proteins showed tissue-distinctive patterns of expression [7]. GLUT1 is the first family member to be recognized, and has been the most broadly investigated. A human SLC2A1 gene that encodes GLUT1 is located on chromosome 1p34.2 [8]. This GLUT1 has an elevated affinity for glucose, and is able to carry glucosamine, galactose, and mannose [9]. GLUT1 is accountable for the uptake of glucose, and it is present in almost all tissues in normal states [8].

The level and location of GLUT1 expression could be an appropriate biomarker of glucose metabolism and hypoxia, which might be assessed easily and economically as part of the histologic assessment practice of neoplasms [10]. Many studies have reported elevated levels of glucose transporter1 expression and associated it with tumor growth, enhanced invasive potential, unfavorable prognosis, and poor

survival in many tumors, including stomach [11], prostate [12], breast [13], colorectal [14], ovarian [15], lung [16], pancreatic [17], esophageal [18], and oral cancers [19].

Therefore, this report will define the expression profile of GLUT1, and examine the relationship between this phenotype and clinicopathologic features of urinary bladder cancer to determine the clinical importance of GLUT1 as a diagnostic marker and an indicator of long-term overall survival in bladder cancer patients.

Materials and methods

The present study recruited 128 paraffin-embedded tissue blocks of histologically-confirmed urinary bladder carcinoma along with their clinicopathological data from the record of the pathology department at the university hospital. A control group of 24 non-cancerous bladder tissue samples was also employed. All slides were reviewed and assessed by two pathologists. All paraffin-embedded tissue blocks of urinary bladder carcinoma and the control group was used for the construction of tissue microarray (TMA) as we described in a previous paper [20]. TMA blocks were cut (four micron thickness), H&E stained and re-evaluated for diagnosis and grading confirmation by two pathologists. This research was executed in the pathology lab over a duration of 12 months and was completed on 24th April 2019.

TMA paraffin blocks of tumor and control groups were sliced at 4 μm thickness. Tissue sections were fitted with coated slides. Immunohistochemistry (IHC) staining was executed in a fully-automated immunostainer (Bench Mark ULTRA, Ventana Medical Systems Inc., Tucson, USA). Paraffin-embedded sections were immersed in xylene for deparaffinization, then were rehydrated. Mild pre-treatment with a cell conditioning solution (Ventana Medical Systems Inc., Tucson, USA) was done for 60 min. GLUT1 Rabbit Polyclonal Primary Antibody (Ventana Medical Systems Inc., Tucson, USA) was added to tissue sections and incubated at 37°C for 16 minutes. The detection kit used was ULTRAVIEW TM DAB visualizing system (Ventana Medical Systems Inc., Tucson, USA). Later tissue slides were gently rinsed, Mayer's haematoxylin counterstained, and mounted. Suitable positive (colorectal carcinoma) and negative control slides were employed as per instruction of the manufacturer.

Tumor sections were counted positive when brown staining is developed in malignant urothelium. Two pathologists analyzed the quality of GLUT1 expression and approximated the percentage of positive neoplastic cells. The estimations of GLUT1 positive cells were determined by semi-quantitative procedure in 3 microscopic fields using 40x lenses. All cases that showed brown stain in less than 5% of tumor cells were counted as negatively stained. Grades of 0, 1, 2, and 3 were assigned for no stain, weak, modest and intense or strong stain respectively. These grades are displayed in this report as positive (1, 2 and 3), and negative (0). The lowest grade recorded by any pathologist was taken into account if a disparity occurred.

Statistical analysis

The data were analysed by using version 21 of IBM-SPSS. All results were displayed as incidences and percentages. The relationship between clinical factors of urinary bladder cancer cases and GLUT1 immunoexpression was investigated by Fisher Exact test. Log-rank test and Kaplan Meier survival curves have been utilized to evaluate the survival distribution pattern of positive GLUT1 tumors with various clinicopathologic factors. The significance limit was set at $P < 0.05$.

Results

Clinical data of all recruited urinary bladder tumors (128: 104 males and 24 females) have been revised and are shown in **Table 1**. In the present study, the most common type of urinary bladder tumor was urothelial carcinoma (82%), and less often the squamous differentiation variant (13.3%), and pure squamous cell carcinoma (4.7%). The age of bladder cancer patients fluctuated between 31 and 93 years with a mean of 62.5 years. Medical records revealed 38 (29.7%) deaths from bladder cancer among the recruited tumor cases. 62 cases showed muscularis propria invasion, 24 cases remote metastases, 22 cases lymph node involvement, and 19 cases had vascular invasion. Sections from both male and female tumor cases showed comparable intensity and diffusenes, of GLUT1 staining pattern.

Table 1. Associations of GLUT1 expression in bladder cancer with various clinicopathologic variables

		GLUT1 expression in malignant urothelial cells				*P*-Value[a]
		Negative		Positive		
		n	(%)	n	(%)	
Gender (Male/Female)	Female	4	(17.4)	19	(82.6)	0.363
	Male	13	(12.4)	92	(87.6)	
Age at Diagnosis (Years)	< 50	1	(6.3)	15	(93.8)	0.219
	50-59	3	(8.3)	33	(91.7)	
	60-69	4	(10.5)	34	(89.5)	
	≥ 70	9	(23.7)	29	(76.3)	
Histotype of Cancer (Urothelial or Squamous)	Squamous	0	(.0)	6	(100.0)	0.999
	Urothelial	15	(14.3)	90	(85.7)	
	Urothelial/Squamous	2	(11.8)	15	(88.2)	
Grade	High Grade	16	(24.2)	50	(75.8)	0.000
	Low Grade	0	(.0)	50	(100.0)	
	Undecided	1	(8.3)	11	(91.7)	
Stage of Disease	0a	0	(.0)	21	(100.0)	0.020
	I	1	(3.2)	30	(96.8)	
	II	8	(22.2)	28	(77.8)	
	III	1	(14.3)	6	(85.7)	
	IV	4	(17.4)	19	(82.6)	
	Undecided	3	(30.0)	7	(70.0)	
Muscularis propria invasion (MIBC or NMIBC)	MIBC	13	(20.3)	51	(79.7)	0.010
	NMIBC	1	(2.2)	45	(97.8)	
	Undecided	3	(16.7)	15	(83.3)	
Lymph Node invasion	Negative	14	(13.2)	92	(86.8)	0.593
	Positive	3	(13.6)	19	(86.4)	
Vascular Invasion	Negative	13	(11.9)	96	(88.1)	0.281
	Positive	4	(21.1)	15	(78.9)	
Metastasis	No	13	(12.5)	91	(87.5)	0.524
	Yes	4	(16.7)	20	(83.3)	

[a]Significance values of Fisher's Exact test.

Increased GLUT1 expression has been found in urinary bladder cancer, and it was found in 111 (86.7%) cases, of which 81 (73%) cases showed high levels (moderate to strong) immunostaining (**Figure 1A-D**). More than 60% of the positive cases showed brown color in more than 40 percent of malignant cells. Only 4 (16.6%) control cases showed weak to moderate positive GLUT1 immunostaining in less than 20% of urothelial cells. Most of the positive tumors (75%) showed moderate cytoplasmic and intense membranous staining, while the remaining tumors revealed diffuse cytoplasmic staining only. GLUT1 immunohistochemical staining was found significantly correlated with low grade, low stages, and in tumors of non-muscularis propria invasion ($P < 0.05$). Positive GLUT1 expression was observed in 100 percent of low-grade cases and was more frequent in stages 0a and I. Most urothelial carcinomas which had no muscularis propria invasion showed positive GLUT1 immunoreactivity. Urinary bladder tumors which developed lymph node involvement, vascular invasion, and metastasis did not show significant associations with GLUT1 expression in their malignant urothelial cells. No significant associations were observed with gender, age, and cancer histotype.

Log rank test (**Table 2**) and Kaplan-Meier survival curves (**Figure 2**) showed significant poor survival in stage III and stage IV patients ($P < 0.05$); mean survival was lowest at 29.924 months in stage IV patients. Similarly, signifi-

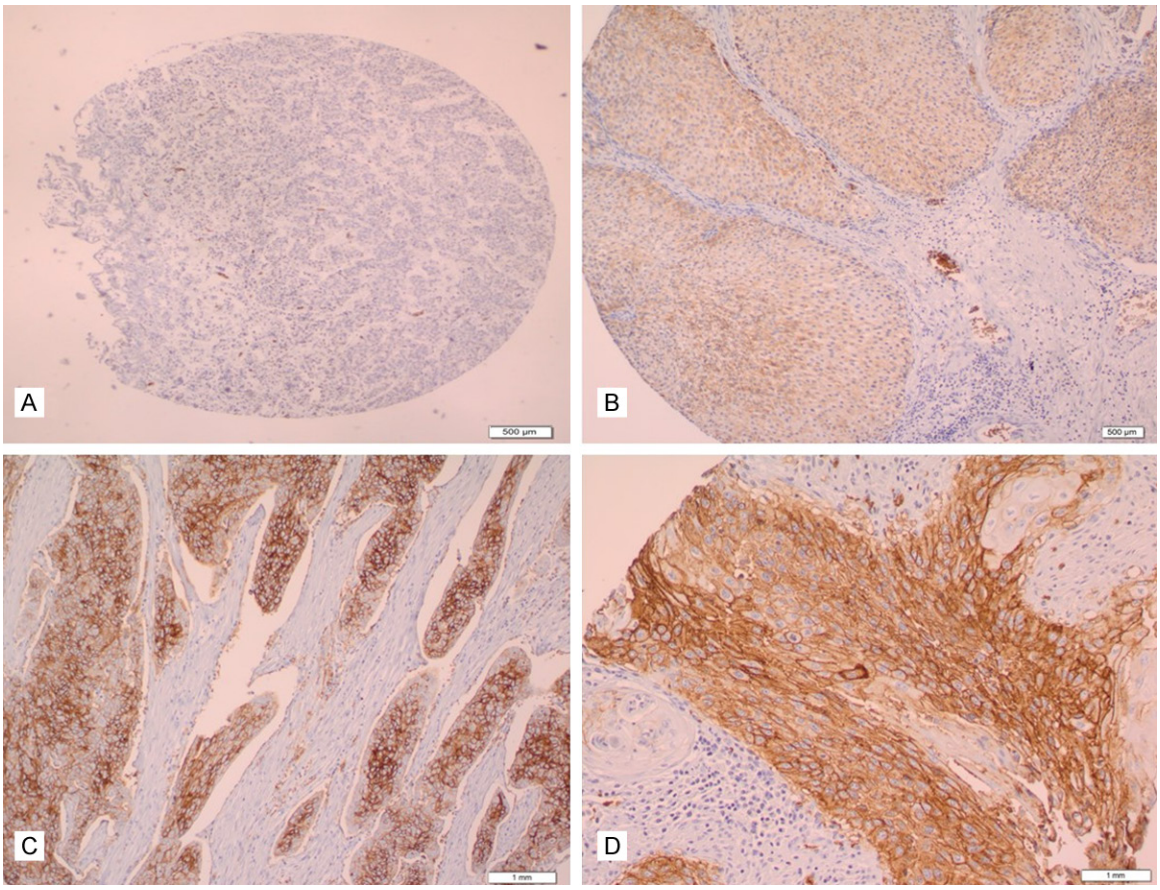

Figure 1. GLUT1 immunostaining patterns in urothelial carcinoma. A. Negative-stained tumor (4X); B. Weak GLUT1 staining in malignant urothelial cells (10X); C. Moderate cytoplasmic and strong membranous GLUT1 staining in malignant urothelial cells (40X). D. Strong membranous GLUT1 staining in malignant urothelium.

cantly better survival was observed in low grade tumors ($P < 0.05$). The survival rate was also significantly higher in cases which did not develop blood vessel invasion or metastasis in lymph node ($P < 0.05$). Also, a significantly poor survival pattern was observed in metastasis-positive cases ($P < 0.05$), and mean survival was significantly less. However, no significantly different survival distributions were observed by GLUT1 expression, age, muscle invasion, and histotype of cancer.

Discussion

Neoplastic cells distinctively display enhanced metabolism with a great necessity for a source of energy, elevated glucose need, and greater glucose influx. Glucose is involved not just in fast ATP assembly, but similarly in biomass buildup through the production of necessary elements for nucleotides, cellular membrane and other constituents involved in cellular division [21]. This surplus energy could be provided by increased oxidative or/and anaerobic glycolytic processes with improved glucose intake. Eugene et al., and Whyard et al. reported increased glucose uptake which led to the multiplication of bladder tumor cells while reduced glucose level decreased cellular proliferation in comparison to control group [22, 23]. Enhanced glucose uptake was correlated with amplified expression of GLUT1, which shows high-affinity for glucose and is frequently overexpressed in all types of cancer [21]. Increased intensity of GLUT1 expression is correlated with poor outcomes in the majority of solid neoplasms, suggesting that GLUT1 expression profile status is an important prognostic marker and auspicious medicinal target in solid neoplasms [24, 25]. Similarly, improved uptake of glucose through increased expression of GLUT1 occurs in urothelial cell carcinoma, this stimulates increased glucose uptake within cells, thus assisting cellular proliferation and survival [26, 27]. Comparable to our findings, remarkably, many studies stated that GLUT1 expression was frequent-

Table 2. Comparison of survival distribution with various clinicopathologic factors in bladder cancer

		n	No. of Events	Mean Survival	Std. Error	*P*-value[a]
Glut 1 expression in epithelial cells	Negative	15	6	40.145	8.011	0.536
	Positive	104	31	86.908	9.659	
Gender	Female	21	8	65.290	15.364	0.459
	Male	98	29	87.719	9.541	
Age at Diagnosis (Years)	< 50	16	4	49.155	8.561	0.218
	50-59	32	7	89.210	12.404	
	60-69	36	14	74.773	14.303	
	≥ 70	35	12	43.419	7.167	
Muscularis propria invasion (MIBC or NMIBC)	MIBC	57	22	62.820	10.176	0.065
	NMIBC	45	10	96.313	14.892	
	Undecided	17	5	72.780	20.968	
Histotype of Cancer	Squamous	5	3	56.353	27.730	0.229
	Transitional	99	28	85.471	10.690	
	Transitional/Squamous	15	6	50.369	19.578	
Disease Stage	0a	20	1	129.770	10.358	0.019
	I	31	9	88.236	15.882	
	II	30	10	68.982	14.330	
	III	7	2	45.967	12.594	
	IV	21	11	29.924	6.830	
	Undecided	10	4	38.690	7.114	
Grade	High	63	22	69.118	12.886	0.001
	Low	46	9	99.735	11.145	
	NA	10	6	51.930	19.707	
Lymph Node	Negative	98	25	93.825	9.909	0.000
	Positive	21	12	24.844	6.453	
Vascular Invasion	Negative	100	28	89.803	9.659	0.001
	Positive	19	9	19.435	4.913	
Metastasis	No	97	26	89.503	10.055	0.030
	Yes	22	11	34.169	6.912	

[a]Significance value for the log-rank test.

ly present in both muscle invasive and nonmuscle invasive urothelial carcinomas; nonetheless, not in benign bladder lesions (papilloma) or normal urothelial cells [27-33]. Furthermore, the Reis et al study revealed that while normal urothelium of bladder progresses to malignancy, expression of GLUT1 increases [34]. Also, the Boyaci and Behzatoğlu study showed increased GLUT1 expression in the nested variant of urothelial carcinoma, and concluded that GLUT1 may be a useful indicator when histological discrimination is not certain between urothelial carcinoma nested variant and benign lesions of the urothelium [33].

In tumors, GLUT1 activity, which is important for glucose influx, is subject to its location in the cellular compartment. Enhanced transfer of GLUT1 to the cellular membrane is considered one of the major factors driving the progression and aggressiveness of tumor cells [21, 35]. Although GLUT1 staining in the present study is predominantly membranous and consistent with the above studies, some changes in GLUT1 location have been observed in some tumor cases. This is consistent with other studies, including ovarian cancer [36] and lymphoma [37]. Yet, no reports about similar changes is present in urologic tumors.

In contrast, conclusions concerning the relationship between GLUT1 phenotype and clinicopathologic factors have been and are still controversial [27, 30, 31, 38, 39]. Unlike our study, some studies reported that GLUT1 protein showed significantly stronger expression in

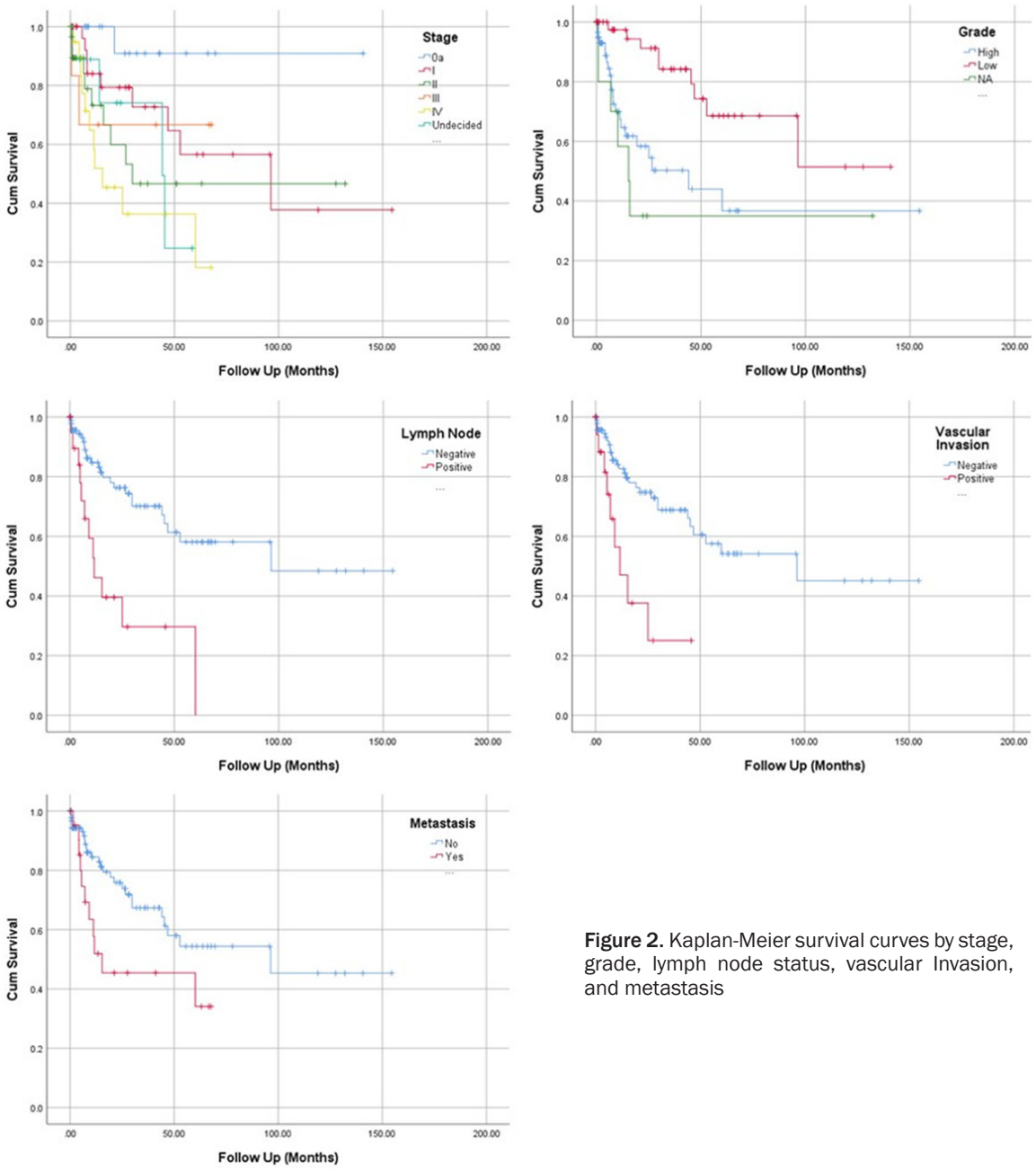

Figure 2. Kaplan-Meier survival curves by stage, grade, lymph node status, vascular Invasion, and metastasis

muscle-invasive tumors in comparison to non-invasive tumors. Moreover, GLUT 1 expression was increased considerably in tumors of high grade or/and stage more than in neoplasms of low grade or/and stage. They concluded that intense GLUT1 staining significantly correlates with progression, aggressiveness, and worse survival in bladder tumors [27, 31]. Zhou et al. and Boström et al. reported similar association with high grade, but not stage or recurrence [30, 32]. On the other hand, our study proposes that the intense GLUT1 staining is inversely associated with bladder tumors of high grade and stage, while Hoskin et al. reported that neither grade nor stage are associated with GLUT1 overexpression [38].

Once malignant cells have gained the ability to invade, at a particular point in anaplasia, such genomic instability andloss of tumor inhibitors,means no further increase of cellular glucose intake can be accomplished [34, 38]; this may elucidate how GLUT1 staining failure distinguishes between high grades and stages with subsequent infiltration in the current research project. Nonetheless, the present study

could not find significant different survival distributions adjusted by GLUT1 expression unlike a few studies, which showed a correlation with worse overall survival [31, 32, 40]. Hoskin et al. stated that GLUT1 increased expression in cancer of the bladder is correlated with tumor progression and poor survival. It is also an independent indicator of overall survival. The rate of five-year survival in patients with strong GLUT1 staining tumors was 32% in comparison with 72% in patients with weak GLUT1 staining tumors [38].

Conclusion

This study's findings confirm the earlier data suggesting that GLUT1 has been frequently overexpressed in bladder urothelial cell carcinoma and may help discriminate malignant bladder tissues from benign tissues. Also, the intensity of GLUT1 expression is significantly inversely correlated with progression of neoplasms and suggestive of an invasive biological behavior. However, the diagnostic and prognostic importance of GLUT1 protein in urothelial tumors requires more study.

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Disclosure of conflict of interest

None.

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