Am J Transl Res 2023;15(2):1510-1516
www.ajtr.org /ISSN:1943-8141/AJTR0147623

Original Article

E-cadherin and FGFR3 are risk factors determining prognosis of patients with bladder urothelial carcinoma

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Received November 9, 2022; Accepted January 13, 2023; Epub February 15, 2023; Published February 28, 2023

Abstract: Objective: To explore the diagnostic value of the combined detection of E-cadherin and FGFR3 in patients with bladder urothelial carcinoma and their correlation with patient prognosis. Methods: The study retrospectively analyzed the case data of 96 patients with bladder urothelial carcinoma treated at the Yixing Guanlin Hospital from June 2018 to June 2020. Tumor tissue of each patient and matched healthy tissue were collected for immunohistochemical staining. Differences in FGFR3 and E-cadherin expression were identified between tumor and healthy tissues. The influence of clinical characteristics on the recurrence was analyzed using a univariate analysis. Then, a multivariate logistic regression analysis was performed to analyze the risk factors for recurrence in patients with bladder urothelial carcinoma. The diagnostic value of FGFR3, E-cadherin and their combination for disease recurrence and prognosis was analyzed. The correlation of FGFR3 and E-cadherin expression with disease recurrence was discussed. Results: The positive expression of FGFR3 in the cancer tissues was significantly higher than that in the adjacent tissue, while the positive expression of E-cadherin showed the opposite ($P<0.05$). Logistic regression analysis showed that tumor size, TNM stage, pathological grade, FGFR3 and E-cadherin were risk factors for the recurrence of bladder urothelial carcinoma ($P<0.05$). The area under the curve of FGFR3 combined with E-cadherin in evaluating prognosis and recurrence was 0.957. Correlation analysis revealed that FGFR3 was significantly and positively correlated with the patients' prognostic recurrence while E-cadherin was negatively correlated with it. Conclusion: FGFR3 and E-cadherin are risk factors affecting the prognosis of patients with bladder urothelial carcinoma, and they are associated with the outcome of bladder cancer.

Keywords: E-cadherin, FGFR3, epithelial-mesenchymal transition of bladder cancer, diagnostic value, prognosis, correlation

Introduction

Bladder carcinoma (BC) is one of the most common malignancies of the urinary system, with its incidence ranking the 4th among male malignant tumors in the United States [1]. In China, the incidence of male BC ranks first among all urogenital malignancies, of which urothelial carcinoma of the bladder is the most common, accounting for over 95% of all BC cases [2]. Infiltration and metastasis are important reasons leading to adverse prognosis and death [3]. Although tumor-node-metastasis (TNM) staging and pathological grading of tumors are routinely used in clinical work to evaluate the probability of postoperative recurrence and metastasis as well as overall survival of patients, the individualized differences of tumors, the different experience of evaluators and the lack of clinicopathological data may lead to inaccurate prognosis assessment [4]. As research into the molecular mechanisms of tumor occurrence and development has intensified over the past decade, a number of molecular markers that play a key role in tumor development have gradually been identified. Meanwhile, studies have found that these markers are closely related to tumor prognosis and can be used as effective means to evaluate the prognosis of bladder uroepithelial carcinoma [5].

Fibroblast growth factor receptor 3 (FGFR3) is the most mutated gene in bladder urothelial carcinoma [6]. Mutations in bladder urothelial carcinoma are associated with recurrence-free survival of patients, but the related studies are limited [7]. Recent research has shown that the

zinc-finger transcription factor Snail can induce epithelial-mesenchymal transition (EMT) by transcriptionally inhibiting E-cadherin expression [8]. However, there are currently few clinical studies in this area. Based on this, we used the streptavidin-peroxidase complex (SP) immunohistochemical staining method to detect the expression of Snail and E-cadherin in bladder urothelial carcinoma and adjacent tissue, aiming to analyze their expression levels and their roles in BC infiltration and metastasis.

This research is innovative and open. First of all, although most of these molecular markers have not been used clinically, they have great potential based on relevant data. Molecular markers will become a reliable and viable tool for evaluating the prognosis of bladder urothelial carcinoma. Although these molecular markers cannot completely replace the traditional prognosis evaluation based on clinical staging and pathological grading, the rational use of FGFR3 and E-cadherin can greatly assist clinicians in assessing the prognosis of tumors.

Materials and methods

General information

The study retrospectively analyzed the case data of 96 patients with bladder urothelial carcinoma treated at the Yixing Guanlin Hospital from June 2018 to June 2020. Tumor tissue in the patients and matched healthy tissue were collected. This study was approved by the Medical Ethics Committee of the Urology Department of Yixing Guanlin Hospital.

Inclusion criteria: (1) Patients who were diagnosed with bladder urothelial carcinoma for the first time; (2) Patients who underwent surgical treatment; (3) Patients with urothelial carcinoma confirmed by postoperative pathology; (4) Patients with complete case data, including laboratory index test records, general data (sex, age, tumor number, tumor size, TNM stage and pathological grade), time of tumor recurrence and progression, and time of death; (5) Patients without other tumors; (6) Patients who were complicated by severe hematological diseases.

Exclusion criteria: (1) Patients who received radiotherapy and chemotherapy before surgery; (2) Patients with other types of tumors; (3) Patients who were pregnant or lactating; (4) Patients with incomplete clinical data; (5) Patients who were lost to follow up.

Examination methods

Pathological specimens of BC patients who had undergone initial surgery (total cystectomy or transurethral resection of bladder tumor) were obtained for paraffin embedding and immunohistochemical staining. The clinical staging and grading of tumors were evaluated according to the American carcinoma Society and World Health Standards [9]. The TNM staging of the tumor was classified as I-III, and the pathological grading was classified as T1-T4.

Immunohistochemical staining

The tissue samples from BC patients were collected and paraffin-sectioned, with a thickness of 4 μm. FGFR3 and E-cadherin protein expression were detected by the standard SP immunohistochemical staining. The tissue slices were processed and incubated with FGFR3 antibody (1:50; Cell Signaling Technology, USA) and E-cadherin antibody (1:400; Cell Signaling Technology, USA) overnight at 4°C. Then, they were incubated with a second antibody (1:400; Cell Signaling Technology, USA) at room temperature for 20 min. The peroxidase labeled streptavidin was then incubated at room temperature for 20 min and stained with Tris HCl solution containing 0.02% 3,9-diaminobenzidine for 5-7 min. Finally, the slices were stained with hematoxylin, washed, dehydrated and sealed for observation and analyses.

Observation indicators

Primary outcome measures: (1) Differences in FGFR3 and E-cadherin expression between cancer tissue and healthy tissue were identified. (2) Univariate analysis of the clinical characteristics was carried out to identify factors affecting relapse in patients with bladder urothelial carcinoma. (3) Multivariate Logistic regression analysis was performed to determine independent risk factors affecting disease recurrence in patients with bladder urothelial carcinoma.

Secondary outcome measures: (1) The diagnostic value of FGFR3 combined with E-cadherin for the prognosis and recurrence in BC patients

Table 1. Comparison of expression of FGFR3 and E-cadherin between the cancerous tissue and the health tissue

Tissue	FGFR3		E-cadherin	
	+	-	+	-
Cancerous tissue (n=96)	80 (83.33)	16 (16.67)	37 (38.54)	59 (61.46)
Health tissue (n=96)	31 (32.29)	65 (67.71)	66 (68.75)	30 (31.25)
χ^2	58.145		23.446	
P	<0.001		<0.001	

FGFR3: Fibroblast Growth Factor Receptor 3.

was discussed. (2) The correlation of FGFR3 and E-cadherin expression with BC prognosis and recurrence was analyzed.

Statistical methods

SPSS 26.0 software was used for data statistical processing. The measurement data were tested for normality and homogeneity of variance, and the normally distributed data were expressed in the form of ($\bar{x} \pm s$). These data were compared between groups by the independent sample t-test and within groups by the paired sample t-test. The counting data were expressed in the form of percentage (%), and chi-square test was applied for comparison. Spearman's correlation was used to determine the correlation between two indicators. Multivariate logistic regression analysis was used to analyze risk factors affecting the recurrence and prognosis. Receiver operating characteristic (ROC) curves were plotted to evaluate the value of FGFR3 and E-cadherin as diagnostic markers for BC. When $P<0.05$, it was considered that the difference was statistically significant.

Results

General information

Of all the subjects, there were 72 males and 24 females with an age range of 41-85 years old (mean: 70.59±5.63). There were 54 cases with a single tumor and 42 with multiple tumors. According to the International Union Against Cancer TNM classification, there were 40 cases of Tis-T1 and 56 cases of T2-T4. The pathological grading of the tumors was assessed by referring to the WHO criteria in 2004, with 34 cases of grade G1 (low-grade malignant-prone urothelial papilloma), 39 cases of grade G2 (low-grade papillary urothelial carcinoma), and 23 cases of grade G3 (high-grade papillary urothelial carcinoma) determined. There were 42 patients with distant metastasis and 54 cases without, as well as 66 patients with recurrence and 30 cases without.

Differences in FGFR3 and E-cadherin expression between cancerous tissue and health tissue

Comparing the difference in FGFR3 and E-cadherin expression, it was found that the positive expression of FGFR3 was markedly higher in the carcinoma tissue than in the paracancerous tissue, while the positive expression of E-cadherin showed the opposite ($P<0.05$), as shown in **Table 1**.

Univariate analysis of clinical characteristics affecting recurrence of BC

According to univariate analysis of the clinical features between patients with and without recurrence, there were significant differences in age, number of episodes, tumor size, TNM stage, pathological grade, FGFR3 and E-cadherin. Patients with age ≥65 years old, multiple episodes, tumor size ≥2, TNM stage T2-T4, pathological grading G3, FGFR3 positive expression, and E-cadherin negative expression were more likely to have recurrence ($P<0.05$). See **Table 2** for details.

Multivariate logistic regression analysis of risk factors for recurrence in patients with bladder urothelial carcinoma

In the multivariate analysis, the recurrence of patients with bladder urothelial carcinoma was assigned as the dependent variable, and age, number of cases, tumor size, TNM stage, pathological grade, FGFR3 and E-cadherin as independent variables, for Logistic regression

Table 2. Univariate analysis of clinical characteristics affecting recurrence of bladder urothelial carcinoma

parameter	Recurrence (N=66)	No recurrence (N=30)	χ^2	*P*
Sex			3.168	0.075
Male (n=72)	46	24		
Female (n=24)	20	4		
age			10.925	0.001
<65 (n=24)	10	14		
≥65 (n=72)	56	16		
Number of tumors			10.002	0.002
Single (n=54)	30	24		
Multiple (n=42)	36	6		
tumor size			6.998	0.008
<2 (n=58)	34	24		
≥2 (n=38)	32	6		
TNM staging			9.482	0.003
Tis-T1 (n=40)	16	24		
T2-T4 (n=56)	40	16		
Pathological grade			16.893	<0.001
G1 (n=34)	10	24		
G2 (n=39)	39	0		
G3 (n=23)	17	6		
FGFR3			5.585	0.018
+ (n=80)	59	21		
- (n=16)	7	9		
E-cadherin			4.031	0.035
+ (n=37)	21	16		
- (n=59)	45	14		

Note: TNM: Tumor-Node-Metastasis; FGFR3: Fibroblast Growth Factor Receptor 3.

Table 3. Multivariate logistic regression analysis of risk factors for recurrence in patients with bladder urothelial carcinoma

Indexes	Results of multivariate decomposition					
	β	*SE*	*Wald*	*OR*	95% *CI*	*P*
Tumor size	0.856	0.625	4.963	0.452	0.336-0.569	0.004
TNM staging	0.790	0.456	12.634	0.361	0.269-0.517	0.003
Pathological grade	0.584	0.613	7.781	0.331	0.087-0.575	0.005
FGFR3	0.775	0.275	10.275	0.512	0.312-0.755	0.001
E-cadherin	0.718	0.353	111.327	0.619	0.307~0.836	0.001

Note: TNM: Tumor-Node-Metastasis; FGFR3: Fibroblast Growth Factor Receptor 3.

model establishment in combination with the actual clinical situation. Logistic regression model analysis showed that tumor size, TNM stage, pathological grade, FGFR3 and E-cadherin were independent risk factors for the recurrence in patients with bladder urothelial carcinoma (P<0.05), as shown in **Table 3**.

The diagnostic value of FGFR3 combined with E-cadherin for the prognosis of BC patients with recurrence

The area under the ROC curve (AUC) of FGFR3 combined with E-cadherin for the prognosis and recurrence of patients with bladder urothelial carcinoma was 0.957, with high specificity and sensitivity. The AUC of the combination was markedly higher than that of single FGFR3 or E-cadherin detection (0.775 and 0.759). There was a statistically significant difference in the analysis and prediction models of the three detection methods (Z= 2.235, *P*<0.05), as shown in **Table 4** and **Figure 1**.

Correlation analysis of FGFR3 and E-cadherin with prognosis and recurrence in patients with bladder urothelial carcinoma

Spearman correlation coefficient analysis of FGFR3 and E-cadherin expression and the recurrence of patients with bladder urothelial carcinoma showed that FGFR3 was positively correlated with prognostic recurrence in patients with bladder urothelial carcinoma (*r*=0.892, *P*< 0.001), while E-cadherin was negatively correlated with it (*r*=-0.871, *P*<0.001). See **Table 5** for details.

Discussion

EMT refers to the transformation of epithelial cells into mesenchymal cells under specific physiological and pathological conditions, characterized by the loss of epithelial cell polarity and the acquisition of mesenchymal properties [10]. Tumor metastasis is an extremely complex multi-step process, which roughly includes the

Table 4. Diagnostic value of FGFR3 combined with E-cadherin for prognosis and recurrence of bladder urothelial carcinoma

index	Accuracy	sensitivity	specificity	Cutoff value (%)	AUC
FGFR3	76.00	77.50	70.26	75.52	0.775 (0.554-0.763)
E-cadherin	71.00	70.00	76.60	73.35	0.759 (0.562-0.847)
Joint detection	97.00	97.50	94.20	93.25	0.957 (0.913-0.969)

Note: FGFR3: Fibroblast Growth Factor Receptor 3.

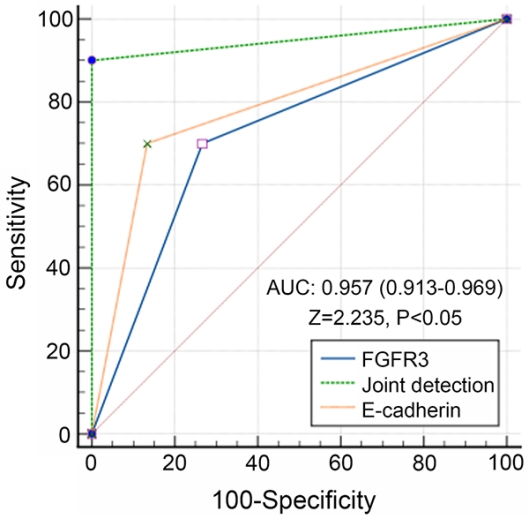

Figure 1. ROC curve of diagnostic value of FGFR3 combined with E-cadherin for prognosis and recurrence in bladder urothelial carcinoma. Note: ROC: Receiver Operating Characteristic; FGFR3: Fibroblast Growth Factor Receptor 3.

Table 5. Correlation analysis of FGFR3 and E-cadherin with prognosis and recurrence of bladder urothelial carcinoma

Indicator	Prognosis Relapse	
	r	*P*
FGFR3	0.892	<0.001
E-cadherin	-0.871	<0.001

Note: FGFR3: Fibroblast Growth Factor Receptor 3.

following steps: tumor cells shedding from the primary site, invading the surrounding tissues, entering the circulatory system, evading immune surveillance, attaching to the distant lumen bed, penetrating into the target organ tissues, and forming secondary tumors [11]. During invasion and metastasis, tumor cells often destroy the specific connection between tumor cells through various mechanisms, so as to reduce the adhesion with surrounding cells and enhance their mobility, thus playing an important role in tumor cell invasion and metastasis [12]. The reduction and loss of E-cadherin can lead to the weakening of cell adhesion, which makes it easy for cancer cells to leave the primary tumor then infiltrate and metastasize [13].

In this study, it was found that with the deepening of tumor invasion and the increase of pathological grading, the positive expression of E-cadherin decreased correspondingly, which is consistent with previous reports [14, 15]. Logistic regression model analysis showed that tumor size, TNM stage, pathological grade, FGFR3 and E-cadherin were independent risk factors for the recurrence of bladder urothelial carcinoma ($P<0.05$). The reason may be that FGFR3 mutation also has a certain impact on tumor recurrence, which is closely related to the prognosis of BC. FGFR3 can participate in EMT of BC, with low tumor heterogeneity and mutation, which is significantly related to patient prognosis [16].

The AUC of FGFR3 combined with E-cadherin in evaluating prognosis and recurrence in patients with bladder urothelial carcinoma was found to be 0.957, with high specificity and sensitivity. The AUC of the combination was markedly higher than that of single FGFR3 or E-cadherin detection. It also suggests that any single index was not good enough for clinical use and cannot temporarily replace the evaluation by clinical and pathological staging for tumor prognosis. Nonetheless, the comprehensive analysis and adjustment of a variety of molecular markers can be combined with clinicopathological staging for evaluating the prognosis of bladder urothelial carcinoma. Molecular markers may even have advantages over the traditional evaluation method [17]. FGFR3 has been shown to be a prognostic and predictive marker and an effective therapeutic target for bladder urothelial carcinoma [18]. The antisense transcript FGFR3-AS1 enhances

the stability and expression of FGFR3 mRNA and overexpresses it in urothelial tumors, which is associated with tumor invasion, proliferation and activity [19]. As a prognostic indicator, FGFR3 gene changes are usually associated with lower grade and stage in all bladder urothelial carcinomas [20]. In addition to this, E-cadherin also plays an important role in maintaining cell morphology, movement and adhesion through its interaction with β-catenin and the actin cytoskeleton. Therefore, the most common change during EMT is the down-regulation of E-cadherin expression on the surface, leading to the loss of homotypic adhesion [21], suggesting the role of E-cadherin as a potential biomarker. In the present study, we found that while both FGFR3 and E-cadherin were of certain diagnostic value, their combined diagnosis was more accurate.

Further, the logistic regression model and the correlation analyses of prognosis pointed out that changes in FGFR3 and E-cadherin indexes were most closely related to tumor prognosis, and the combined application of these two indexes could more effectively and accurately predict the prognosis of patients with bladder urothelial carcinoma [22]. Also, due to different mechanisms of these two molecular markers, they complement each other and can provide more effective information that may even be better than the traditional prognosis prediction methods by tumor clinical staging and pathological grading [23, 24].

Although this study has obtained certain research results, it still has certain limitations. There may be some certain bias in the results due to the small sample size, with only 96 patients included, and the nature of retrospective analysis. Therefore, a larger sample size is needed in future studies to further confirm the diagnostic value of FGFR3 and E-cadherin in bladder urothelial carcinoma.

Conclusion

To sum up, FGFR3 and E-cadherin are risk factors affecting the prognosis of patients with bladder urothelial carcinoma, and they are strongly associated with recurrence and prognosis in the patients. In addition, the combined detection of FGFR3 and E-cadherin expression can be used as a diagnostic tool for the recurrence of bladder urothelial carcinoma, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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References

[1] Jing P, Zhao N, Xie N, Ye M, Zhang Y, Zhang Z, Li M, Lai X, Zhang J and Gu Z. miR-24-3p/FGFR3 signaling as a novel axis is involved in epithelial-mesenchymal transition and regulates lung adenocarcinoma progression. J Immunol Res 2018; 2018: 2834109.

[2] Shenoy S. CDH1 (E-cadherin) mutation and gastric cancer: genetics, molecular mechanisms and guidelines for management. Cancer Manag Res 2019; 11: 10477.

[3] Brunetti B, Foglia A, Savini F, Dondi F and Abbate JM. Inverted urothelial papilloma in a cat. Vet Pathol 2022; 59: 138-142.

[4] Dochiț CM, Stepan AE, Mărgăritescu C, Florescu MM and Simionescu CE. Immunoexpression of E-, P- and N-cadherins in ovarian serous malignant tumors. Rom J Morphol Embryol 2019; 60: 1215-1219.

[5] Zeng T, Peng L, Chao C, Fu B, Wang G, Wang Y and Zhu X. miR-451 inhibits invasion and proliferation of bladder cancer by regulating EMT. Int J Clin Exp Pathol 2014; 7: 7653.

[6] Harsanyi S, Ziaran S, Bevizova K, Trebaticky B, Bujdak P, Galbavy S and Danisovic L. The prognostic value of E-cadherin and Ki-67 compared to standard histopathologic examination in non-muscle invasive bladder cancer. Bratisl Lek Listy 2020; 121: 444-449.

[7] Li Y, Zhang K, Yang F, Jiao D, Li M, Zhao X, Xu C, Liu S, Li H, Shi S, Yang B, Yang L, Han D, Wen W and Qin W. Prognostic value of vascular-expressed PSMA and CD248 in urothelial carcinoma of the bladder. Front Oncol 2021; 11: 771036.

[8] Goutas D, Tzortzis A, Gakiopoulou H, Vlachodimitropoulos D, Giannopoulou I and Lazaris AC. Contemporary molecular classification of urinary bladder cancer. In Vivo 2021; 35: 75-80.

[9] Nassar AH, Lundgren K, Pomerantz M, Van Allen E, Harshman L, Choudhury AD, Preston MA, Steele GS, Mouw KW, Wei XX, McGregor BA, Choueiri TK, Bellmunt J, Kwiatkowski DJ and Sonpavde GP. Enrichment of FGFR3-TACC3 fusions in patients with bladder cancer

who are young, Asian, or have never smoked. JCO Precis Oncol 2018; 2: PO.18.00013.
[10] Skarkova V, Skarka A, Manethova M, Stefanidi AA and Rudolf E. Silencing of E-cadherin expression leads to increased chemosensitivity to irinotecan and oxaliplatin in colorectal cancer cell lines. Hum Exp Toxicol 2021; 40: 2063-2073.
[11] Agrawal V and Bharti N. Alterations in expression of cell surface and cell cycle signaling molecules in recurrent nonmuscle invasive bladder cancers: a tissue microarray expression analysis. 2018.
[12] Assidi M, Jafri MA, Abu-Elmagd M, N Pushparaj P, Saddick S, Messaoudi S, Alkhatabi H, Al-Maghrabi J, Anfinan N, Sait M, El Omri A, Sait H, Basalamah H, Buhmeida A and Sait K. Prognostic value of E-Cadherin and its tumor suppressor role in Saudi women with advanced epithelial ovarian cancer. Libyan J Med 2021; 16: 1994741.
[13] Morita N, Uemura H, Tsumatani K, Cho M, Hirao Y, Okajima E, Konishi N and Hiasa Y. E-cadherin and α-, β- and γ-catenin expression in prostate cancers: correlation with tumour invasion. Br J Cancer 1999; 79: 1879-1883.
[14] Han Y, Song C, Zhang T, Zhou Q, Zhang X, Wang J, Xu B, Zhang X, Liu X and Ying X. Wilms' tumor 1 (WT1) promotes ovarian cancer progression by regulating E-cadherin and ERK1/2 signaling. Cell Cycle 2020; 19: 2662-2675.
[15] Li H, Zhang Q, Shuman L, Kaag M, Raman JD, Merrill S, DeGraff DJ, Warrick JI and Chen G. Evaluation of PD-L1 and other immune markers in bladder urothelial carcinoma stratified by histologic variants and molecular subtypes. Sci Rep 2020; 10: 1-9.
[16] Apollo A, Ortenzi V, Scatena C, Zavaglia K, Aretini P, Lessi F, Franceschi S, Tomei S, Sepich CA, Viacava P, Mazzanti CM and Naccarato AG. Molecular characterization of low grade and high grade bladder cancer. PLoS One 2019; 14: e0210635.
[17] Yang J, Antin P, Berx G, Blanpain C, Brabletz T, Bronner M, Campbell K, Cano A, Casanova J, Christofori G, Dedhar S, Derynck R, Ford HL, Fuxe J, García de Herreros A, Goodall GJ, Hadjantonakis AK, Huang RYJ, Kalcheim C, Kalluri R, Kang Y, Khew-Goodall Y, Levine H, Liu J, Longmore GD, Mani SA, Massagué J, Mayor R, McClay D, Mostov KE, Newgreen DF, Nieto MA, Puisieux A, Runyan R, Savagner P, Stanger B, Stemmler MP, Takahashi Y, Takeichi M, Theveneau E, Thiery JP, Thompson EW, Weinberg RA, Williams ED, Xing J, Zhou BP and Sheng G; EMT International Association (TEMTIA). Guidelines and definitions for research on epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 2020; 21: 341-352.
[18] Kacew A and Sweis RF. FGFR3 alterations in the era of immunotherapy for urothelial bladder cancer. Front Immunol 2020; 11: 575258.
[19] Liao X, Chen J, Liu Y, He A, Wu J, Cheng J, Zhang X, Lv Z, Wang F and Mei H. Knockdown of long noncoding RNA FGFR3-AS1 induces cell proliferation inhibition, apoptosis and motility reduction in bladder cancer. Cancer Biomark 2018; 21: 277-285.
[20] Pietzak EJ, Bagrodia A, Cha EK, Drill EN, Iyer G, Isharwal S, Ostrovnaya I, Baez P, Li Q, Berger MF, Zehir A, Schultz N, Rosenberg JE, Bajorin DF, Dalbagni G, Al-Ahmadie H, Solit DB and Bochner BH. Next-generation sequencing of nonmuscle invasive bladder cancer reveals potential biomarkers and rational therapeutic targets. Eur Urol 2017; 72: 952-959.
[21] Peinado H, Olmeda D and Cano A. Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype? Nat Rev Cancer 2007; 7: 415-428.
[22] Zhou Q, Chen S, Lu M, Luo Y, Wang G, Xiao Y, Ju L and Wang X. EFEMP2 suppresses epithelial-mesenchymal transition via Wnt/β-catenin signaling pathway in human bladder cancer. Int J Biol Sci 2019; 15: 2139.
[23] Cavallari I, Ciccarese F, Sharova E, Urso L, Raimondi V, Silic-Benussi M, D'Agostino DM and Ciminale V. The miR-200 family of microRNAs: fine tuners of epithelial-mesenchymal transition and circulating cancer biomarkers. Cancers 2021; 13: 5874.
[24] Du Y, Miao W, Jiang X, Cao J, Wang B, Wang Y, Yu J, Wang X and Liu H. The epithelial to mesenchymal transition related gene calumenin is an adverse prognostic factor of bladder cancer correlated with tumor microenvironment remodeling, gene mutation, and ferroptosis. Front Oncol 2021; 11: 683951.