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Original article

Prognostic value of UTX expression in patients with clear cell renal cell carcinoma

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Abstract

Purpose: Our previous studies have identified an abnormal H3K27 methylation status in clear cell renal cell carcinoma (ccRCC). Ubiquitously transcribed tetratricopeptide repeat on chromosome X (UTX) has been demonstrated as a histone demethylase that specifically targets di-methyl groups and tri-methyl groups on lysine 27 of histone H3 (H3K27me2/3). Herein, we explored the prognostic value of tumoral UTX expression in patient with ccRCC.

Patients and methods: We retrospectively enrolled 290 ccRCC patients underwent nephrectomy at a single institution between 2005 and 2007. UTX expression was assessed by immunohistochemistry on tissue microarrays and its prognostic value was assessed using Kaplan-Meier method and Cox proportional hazard model. Nomograms were generated as prediction models for overall survival (OS) and disease free survival (DFS).

Results: Low expression of UTX was associated with reduced OS ($P < 0.001$) and DFS ($P = 0.001$). In multivariate cox analyses, UTX was defined as an independent prognostic factor for OS (hazard ratio = 2.732 [95% CI: 1.650–4.493], $P < 0.001$) and DFS (hazard ratio = 1.959 [95% CI: 1.153–3.326], $P < 0.001$) as well. After stratifying patients into different risk groups using the Mayo Clinic stage, size, grade and necrosis/Leibovich score, decreased UTX expression was associated with shorter OS in both low-risk ($P = 0.002$) and high-risk groups ($P = 0.030$), but with shorter DFS only in low-risk group ($P < 0.001$). Overall, 2 nomograms incorporating UTX expression with other parameters performed well in predicting patients' 5-year and 8-year OS and DFS (c-indices = 0.824 and 0.798, respectively).

Conclusions: UTX is a prognostic biomarker for patients with ccRCC both in OS and DFS prediction, especially significant in low-risk patients.

Keywords: Clear cell renal cell carcinoma; Ubiquitously transcribed tetratricopeptide repeat on chromosome X; Overall survival; Disease free survival; Prognostic biomarker; Nomogram

1. Introduction

Renal cell carcinoma (RCC) is the eighth most common cancer in the USA and accounts for 2% to 3% of all malignancies in adults [1]. The predominant subtype of RCC is clear cell renal cell carcinoma (ccRCC) [2]. RCC is known for its multiresistance to conventional cancer therapies and those patients with localized diseases often experience recurrences after curative surgeries [3]. TNM stage [4], Fuhrman grade [5], Mayo Clinic stage, size, grade, and necrosis (SSIGN) score [6] and the University of California Integrated Staging System [6] might be used to evaluate the prognosis of patients with RCC to some extent,

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whereas these parameters are not entirely reliable [7]. In the era of precision medicine, it is expected that a combination of specific RCC biomarkers into conventional clinicopathological characteristics would allow better prediction of prognosis [8].

Aberrant epigenetic regulation can alter cell fates and result in unrestrained cell growth, leading to cancer development [9]. Over the last years, deregulated histone methylation became a major theme in cancer biology researches including the balance of H3K27 methylation [10,11]. Polycomb group-dependent H3 lysine 27 trimethylation (H3K27me3) has been reported to be related to inactivation of tumor suppressor genes in many human carcinomas [11], including RCC [12], implying its role in carcinogenesis. Ubiquitously transcribed tetratricopeptide repeat on X chromosome (UTX) functions as a histone demethylase toward di-methylated and tri-methylated histone H3 on lysine 27 (H3K27me2/H3K27me3) [13].

Genome-wide analyses have identified various somatic mutations and deletions of UTX in several human cancers, including breast, bladder, prostate and renal cancers, and leukemia [14–16]. Evidences of UTX function in cancers have also been accumulating. In T-cell acute lymphoblastic leukemia, UTX acts as a gender-specific tumor suppressor [17]. In breast cancer, UTX inhibits cancer stem cell properties by repression of epithelial-mesenchymal transition genes [18]. In RCC, UTX is up-regulated in tumor tissues and the expression of UTX is associated with pathological grade [19]. Taking all these evidence together, we wonder whether UTX would associate with patients' outcomes with ccRCC.

Herein, by immunohistochemistry, we evaluated the relationship between UTX expression and the survival of 290 patients with ccRCC. We also evaluated the prognostic value of UTX expression for overall survival (OS) and disease free survival (DFS) after stratifying patients into different risk groups using SSIGN score or Leibovich score. Overall, 2 nomograms integrating this molecule with other clinical parameters were formed to predict patients' OS and DFS.

2. Patients and methods

2.1. Patients

We retrospectively enrolled 290 patients with ccRCC who underwent nephrectomy in the Department of Urology, Zhongshan Hospital, Fudan University between January 2005 and June 2007. Ethical ratification was authorized by the Clinical Research Ethics Committee of Zhongshan Hospital, Fudan University (Shanghai, China) with the approval number B2015-030 in Feb 2015 and informed consent was obtained from each patient. Inclusion criteria were patients with ccRCC, treated with nephrectomy alone, no history of other malignancy and with available fixed tumor tissue. Exclusion criteria were mixed-type renal cancer, bilateral renal cancer, tumor necrosis area $>80\%$ or those with perioperative mortalities.

Patients' clinical and outcome data were updated every 3 months till January 30, 2015 and The median follow-up for all available patients was 99.10 months (range: 2.63–120.47 mo). Each patient's age, gender, tumor size, TNM stage, Fuhrman grade, tumor necrosis, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) information were obtained and listed in Table 1. All tumors

Table 1
Clinicopathological characteristics of patients according to UTX expression

Characteristics	Patients		UTX expression		
	n	%	low	high	*P* value
All patients	290	100	147	143	
Age, y[a]	range	15–86			0.640[b]
≤55	144	49.7	71	73	
>55	146	50.3	76	70	
Gender					0.681[b]
Female	88	30.3	43	45	
Male	202	69.7	104	98	
Tumor size, cm[a]					0.070[b]
≤4	165	56.9	76	89	
>4	125	43.1	71	54	
T classification					0.265[c]
T1	185	63.8	87	98	
T2	27	9.3	13	14	
T3	75	25.9	45	30	
T4	3	1.0	2	1	
N classification					0.242[b]
N0	288	99.3	147	141	
N1	2	0.7	0	2	
Distant metastasis					0.459[b]
No	275	94.8	138	137	
Yes	15	5.2	9	6	
TNM stage					0.430[c]
I	179	61.7	85	94	
II	23	7.9	11	12	
III	70	24.1	40	30	
IV	18	6.2	11	7	
Fuhrman grade					**0.039**[c]
1	31	10.7	10	21	
2	214	73.8	109	105	
3	42	14.5	27	15	
4	3	1.0	1	2	
Necrosis					0.925[b]
Absent	250	86.2	127	123	
Present	40	13.8	20	20	
ECOG PS					0.061[b]
0	213	73.4	115	98	
≥1	77	26.9	32	45	

P-value <0.05 marked in bold font shows statistical significance.
[a]Split at median.
[b]χ^2 test or Fisher's exact test.
[c]Cochran-Mantel-Haenszel χ^2 test.