

Elevation of serum tumor markers caused by hydronephrosis due to upper tract urothelial carcinoma

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Research article

Keywords: upper tract urothelial carcinoma; serum tumor marker; hydronephrosis; tumor metastasis.

Posted Date: November 16th, 2019

DOI: <https://doi.org/10.21203/rs.2.17409/v1>

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Abstract

The aim of this study was to explore the association of changes in classic serum tumor markers and pathological and clinical manifestations of upper tract urothelial carcinoma (UTUC) and to analyze its possible mechanism. A retrospective, descriptive analysis was performed in consecutive patients who were diagnosed UTUC during 2014 – 2018 year in our hospital. Detection of classic serum tumor markers (CSTMs, including CA199, CA242, CA724, CA125, CEA, AFP and SCC-Ag) and pathological manifestations of tumor was collected. The status of hydronephrosis caused by tumor, tumor load and the expressions of CA199, CA724 and CEA in UTUC was also analyzed. Higher rate of abnormal changes in CSTM was found in UTUC patients and it could be dropped off after surgical treatment. There was a correlation between UTUC and the classic serum tumor markers including CA199, CA242, CA724 and CEA. Tumor metastasis and hydronephrosis induced by tumor may be two independent reasons which caused this phenomenon. Immunohistochemistry technology proved CA199, CA724 and CEA were almost expressed in almost all UTUC tissues. We suggested a hypothesis that the pressure acting on tumor caused by hydronephrosis may extrude tumor markers produced from UTUC into blood and even promote metastasis. This may be helpful for distinguished the upper urinary tract tumor without definite diagnosis.

Background

Urinary epithelial transitional cell carcinoma (TCC) includes renal pelvic cancer, ureteral cancer, bladder cancer, and urinary tract cancer. Among them, most studies aimed at finding a prognostic index focused on bladder carcinoma. A variety of biomarkers, such as FGFR3, p53, pRb, p21, Ki67 and VEGF, were used as prognostic factors for bladder cancer in previous studies [1-5]. And even some genomic biomarkers were proposed in recent researches [6, 7]. However, only a few established prognostic factors were found to effectively assess the tumor progression of upper tract urothelial carcinoma (UTUC) [8]. On the other hand, some classic serum tumor markers such as carbohydrate associated cancer antigen 199 (CA199), cancer antigen 125 (CA125), carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP), which were widely used for the diagnosis of different types of gastrointestinal cancer[9], seem to have more prognostic functions. In this study, we detected 7 classic serum tumor markers (CSTM, including CA199, CA242, CA724, CA125, CEA, AFP and SCC-Ag) in 40 patients with UTUC, 37 patients with non-tumoral hydronephrosis, and 44 patients with renal cell carcinoma. We attempted to explore the association between classic serum tumor markers and tumor progression of UTUC, and tried to explain this phenomenon.

Methods

Ethics statement

This study was performed in compliance with the Helsinki Declaration and according to the protocol approved by the Medical Ethics Committee of Ruijin Hospital North affiliated to Shanghai Jiao Tong

University School of Medicine. All participants were informed of the study and gave voluntary, signed informed consent.

Study subjects

A total of 121 patients were included into this retrospective, descriptive analysis. 40 consecutive patients who were diagnosed UTUC during the year 2014 – 2018 in our hospital was performed in this analysis (the age was 69.08 ± 8.42 years, 31 males, 9 females). 37 consecutive patients with non-tumoral hydronephrosis who was diagnosed unilateral renal dysfunction (the age was 53.52 ± 15.90 years, 18 males, 19 females) and 44 consecutive patients with renal cell carcinoma (the age was 56.14 ± 11.89 years, 34 males, 10 females) who were detected classic serum tumor biomarkers were collected as control. All UTUC diagnoses were confirmed pathologically by tissue biopsy. Of the 40 UTUC cases, 22 occurred in the ureter, 18 occurred in the renal pelvis. Bladder TCC were found at the same time in 7 cases. All UTUCs were occurred unilaterally (left 25, right 15). None of the UTUC patients had received radiotherapy, chemotherapy, or endocrine therapy before. Tumor metastasis occurred in 6 out of the 40 UTUC patients (5 ureteral TCCs and 1 renal pelvic TCC, including 3 cases with adjacent lymph node (LN) metastasis, 3 with distal LN metastasis, and 4 with observable organic metastasis). Metastatic UTUC included 5 patients with metastasis occurring at the first diagnosis and 1 patient with postoperative metastasis. 19 UTUC patients of all underwent operation in our hospital and CSTMs changes were compared before and after surgery. Serum CA199, CA242, CA724, CA125, CEA, AFP and SCC-Ag were detected after upper urinary tract space-occupying lesions diagnosed.

Detection of serum tumor markers

Serum CA199, CA242, CA724, CA125, CEA, AFP and SCC-Ag levels were detected by electrochemiluminescence immunoassay (Cobas; Roche Diagnostics, Germany) at the Department of Urology of Ruijin Hospital North affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. The number of abnormal changes in CSTM was counted as an independent index which ≥ 1 was considered as positive. The normal reference values were as follows: CA199 < 35 U/ml, CA242 < 20 IU/ml, CA724 < 8.2 U/ml, CA125 < 35 U/ml, CEA < 5 ng/ml, AFP < 9 ng/ml, SCC-Ag < 1.5 ng/ml.

Measurement data

All patients received triphasic enhanced dynamic CTU scanning. A neoplasm consisting of tumor cells obstructed calyce or ureter, leading to a focal hydronephrosis. The dilation of hydronephrosis was assessed as hydrop length (HL) using the border diameter between extrarenal and intrarenal renal pelvis (for ureteral TCC) or longest diameter of hydrop renal calyce (for renal pelvic TCC) measured in kidney CT

scanning (Figure 1). Tumor load was assessed by tumor volume calculating with the maximum tumor dimension in three orthogonal planes (length, width, and height measuring from kidney CT scanning image or surgical specimen). Calculating formula is $\times \text{Length} \times \text{Width} \times \text{Height}$ [10].

Immunohistochemistry technology

Immunohistochemical staining of CA199, CA724 or CEA was performed to UTUC tissues of 4 patients picked randomly. The specimens were fixed in 10% buffered formalin, embedded in paraffin and cut into 5 μm sections. Automatic immunohistochemical instrument (LeicaBOND III, Australia) was used for immunohistochemical staining according to the instructions. CA 199 (Leica, Art.201902001, England) CA 724 (Abcam, ab199002, USA) and CEA (Leica, Art.201809001, England) were used for staining respectively. Light microscopy was used for observation at a magnification of $\times 100$.

Statistical analysis

The status of hydronephrosis and the level of each CSTM were expressed as mean \pm SD. Measurement data between groups were compared with the t test or Chi-square test (for categorical variables). Statistical analysis was performed using SAS version 8 statistical software and artwork was created with GraphPad Prism version 6. All tests were two-tailed (some tests were showed one-tailed as well) and $P < 0.05$ was considered statistically significant.

Results

The abnormal changes in CSTMs were severer in UTUC patients and it could be dropped off after surgical treatment

We analyzed all abnormal changes of CSTM in UTUC, simple hydronephrosis with no carcinoma and renal cell carcinoma patients. The positive rate of abnormal changes in CSTM was higher in UTUC patients than that in other two groups (Table 1). We especially take a comparison between ureteral TCC and simple hydronephrosis with no carcinoma patients as they shared same characteristic on hydronephrosis. We found that although hydrops of renal pelvis in simple hydronephrosis patient was more serious than that in ureteral TCC patient, the positive rate of abnormal CSTM changes in ureteral TCC showed significantly higher than that in simple hydronephrosis (Table 2). These results indicated that UTUC was a leading cause of abnormal CSTM changes but not the hydronephrosis or other renal tumor.

Totally 19 UTUC patients had underwent surgical treatment in our hospital. CSTMs changes in these patients before and after surgery were compared (Table 3). We found the number of abnormal CSTM changes was decreased after surgery ($P = 0.02$). The rate of abnormal CSTM changes was decreased but

with no statistical significance, which may be due to that just one indicator was abnormal would seem as positive even if actual value had dropped.

UTUC pathological progression may effect abnormal CSTM changes

Tumor metastasis were confirmed by CT scanning, including invasion of adjacent tissues and lymph node metastasis. UTUC patients were divided into four groups according to metastasis status and tumor site: non-metastasis ureteral TCC, non-metastasis renal pelvic TCC, metastasis ureteral TCC, metastasis renal pelvic TCC. As presented in the Table 4, rate of abnormal changes in the CSTMs was found in metastatic UTUC patients (6 in 6, 100%) and non-metastatic UTUC patients (18 in 34, 51.43%) with statistically difference between two groups (one side $P = 0.04$). These results suggested that UTUC metastasis may exist correlation with abnormal CSTM changes.

As all metastasis UTUC patients presented abnormal CSTM changes, we analyzed the effect of tumor grade and tumor infiltration on CSTM changes in non-metastasis UTUC patients. According to the result of tissue biopsy, patients were divided into four groups: low grade UTUC, high grade UTUC, non-infiltrative UTUC, infiltrative UTUC. As presented in the Table 5, for non-metastatic UTUC patients, the rate of abnormal changes in CSTMs in low grade UTUC was significantly increased than that in high grade UTUC ($P = 0.02$), as well as higher in non-infiltrative UTUC than that in infiltrative UTUC ($P = 0.02$). These results suggested that low tumor grade may promote abnormal CSTM changes, and non-infiltrative tumor may had stronger effect on rising CSTM levels.

The association between tumor load and CSTM levels (Table 6) in UTUC patients was assessed. The linear regression analysis result showed no statistical significance between the tumor load and the number of abnormal CSTM changes in non-metastatic UTUC cases ($P = 0.35$).

Hydronephrosis may be one factor on abnormal CSTM changes

We tried to find the association between hydronephrosis status and abnormal CSTM changes in non-metastasis UTUC patients (Table 7). A positive correlation existed between the severity of hydronephrosis and the number of abnormal CSTM changes in non-metastatic ureteral TCC ($P = 0.01$) and in non-metastatic renal pelvic TCC ($P = 0.03$). Hydrop length (HL) was measured for hydronephrosis assessing by CT scan which were described in methods. The linear regression analysis on the status of hydronephrosis and the number of abnormal CSTM changes in non-metastatic ureteral TCC and renal pelvic TCC even given formulas: Number of abnormal CSTM changes = $-0.2369 + 0.0456 \times HL$ ($P = 0.01$) and $-0.0837 + 0.0364 \times HL$ ($P = 0.03$). The linear regression equation between the status of hydronephrosis and the abnormal CSTM in non-metastatic UTUC was: Number of abnormal changes in CSTM = $-0.1869 + 0.0437 \times HL$ ($P < 0.0001$). These results indicated that hydronephrosis status induced by UTUC may have effect on rising CSTM levels.

It seemed that hydronephrosis status and tumor metastasis both played a role on abnormal CSTM changes, a comparison was carried out between both of them. The status of hydronephrosis showed difference between metastatic UTUC patients (32.91 ± 20.06 mm) and non-metastatic UTUC patients (23.22 ± 14.58 mm), but without statistical significance (Table 8, $P = 0.35$). This suggested that hydronephrosis status and tumor metastasis were both independent contributing factors.

Serum level of CA199, CA242, CA724 and CEA may be helpful for UTUC prognosis

We showed all 7 CSTM testing results and status of hydronephrosis in Table 9. There is no abnormal result of CA125 or AFP in UTUC patients, so no comparison was did in this table. A linear regression analysis was used between the status of hydronephrosis and each CSTM level. There were obvious positive correlation between the status of hydronephrosis and the serum level of CA199 ($P = 0.001$) and CA242 ($P = 0.006$) in non-metastasis ureteral TCC patients. An obvious positive correlation was existed between the status of hydronephrosis and the serum level of CA724 ($P = 0.0006$) and CEA ($P = 0.006$) in non-metastasis renal pelvic TCC patients. However, in all, the linear regression analysis showed that the status of hydronephrosis was positively corrected with the serum level of CA199 ($P < 0.0001$), CA242 ($P = 0.0001$) and CA724 ($P = 0.04$). According to these results, it seemed that serum level of CA199, CA242, CA724 and CEA may be helpful for UTUC prognosis.

CA199, CA724 and CEA were expressed in almost all UTUC tissues

The expressions of CA199, CA724 and CEA in UTUC tissues were as anti-CA242 antibody was failed to obtained. 4 different UTUC tissues of patients were picked randomly from participates included in this study. As showed in figure 2, Almost all UTUC tissues were expressing CA199, CA724 and CEA more or less. This may verified the abnormal levels of CSTMs may be originated from UTUC tissues.

Discussion

Classic serum tumor makers (CSTMs, including CA199, CA242, CA724, CA125, CEA, AFP and SCC-Ag) had been one of the most important indicators for predicting and monitoring the residual and recurrent of tumor. Actually, except SCC-Ag were used for squamous cell carcinoma predicting [11, 12], all other CSTMs were related with digestive system cancer or reproductive cancer [13-17]. However, some unconventional roles were played in CSTMs: CEA and SCC-Ag were used for lung cancer diagnosis and prognosis [18, 19]; CA125 and CA199 was reported as significant markers of endometrium pathology [20]; SCC-Ag had a fair diagnostic value for hepatocellular carcinoma [21]. These meant that CSTMs may have more unique values for diagnosis and prognosis of diseases. However, among these 7 CSTMs, only CEA had been reported as early sign of malignancy in urotheliomas of the upper urinary tract and closely related to the recurrence and survival [22, 23]. Some indicators like CxBladder monitor, UroVysion, NMP-22

and bladder tumor antigen were used in diagnosis and monitoring of UC, however, few biomarkers achieve high sensitivity and specificity [24]. The expensive and time-consuming nature was also restricted new methods' developments. On the other hand, UTUC showed several different characteristics compared to bladder cancer at molecular mechanisms underlying tumor development and progression or tumor behavior[25, 26]. Upon these, there is no clinical recognized indicator for diagnosis and prognosis of UTUC.

In our study, we found some of CSTMs existed correlation with UTUC, which may help urologists to assessed mass-like lesions in renal pelvis and ureter . Although indicators of change are not the same in renal pelvic TCC or ureteral TCC, the number of changes in CSTMs showed well-predicting use. Tumor load seemed like no relationship with abnormal CSTMs. Abnormal CSTMs changes existed in all metastatic UTUC patients. Interestingly, in non-metastatic UTUC patients, the rate of abnormal changes in CSTMs in low grade UTUC was significantly increased than that in high grade UTUC, but higher in non-infiltrating UTUC than that in infiltrating UTUC. Low grade carcinoma and tumor infiltration were two indicators of poor prognosis, but take contrary conclusions about abnormal CSTMs changes. There may be other special factor which could induce abnormal CSTMs changes. We proposed pressure caused by hydronephrosis could be one reasonable factor.

We found a positive correlation existed between the severity of hydronephrosis and the number of abnormal CSTM changes in UTUC. A liner regression formula was even taken, although it may because of low number of cases, which showed the positive correlation was strong. Previous studies have shown that the severity of hydronephrosis was associated with increased risk and poor survival in UTUC patients[27, 28], but no research proposed further reason. Almost all UTUC tissues were expressing CSTMs more or less. Our research found hydronephrosis may effect CSTM changes, especially in non-metastatic UTUCs. Pressure hypothesis could explain phenomenon upon. In tumor patients, classic tumor biomarkers not only represented characteristics of specific tumors, but also seemed to be associated with certain prognostic markers[29]. So for metastatic UTUC patients, some of CSTMs could rise without specificity. But for non-metastatic UTUC patients, classic tumor biomarkers produced by carcinoma cells was not easy to get into blood. As hydronephrosis induced by UTUC became more and more serious, the pressure not only dilated renal pelvis and ureter but also caused compression on tumor, which may induce nonspecific elevation of CSTMs. This could also explain why abnormal CSTMs changes were less in non-infiltrating UTUC patients than that in infiltrating UTUC patients: non-infiltrating carcinoma was often exophytic growth which could induced more serious hydronephrosis. Furthermore, also there was no direct evidence showed that high pressure in renal pelvis and ureter caused by transitional cell carcinoma in upper urothelial tract may increase the risk of tumor metastasis, urologists should be vigilant on this possibility.

There are some limitations in our study. First, the sample size in this research was small as our hospital has just been established for 5 years and cases accumulation was limited. Further accumulation of cases and accurate researches should be carried out to confirm results upon. Second, as not all UTUC patients accepted surgery therapy and limited cases size, analysis of CSTMs changes before and after

surgical treatments was oversimplify, and only a few tissues of patients were accepted immunohistochemistry stain. We used CT scanning result to assessed the severity of hydronephrosis but it could not be reflect the pressure in renal pelvis and ureter in accuracy. The results must be validated in large, independent cohorts before it can be applied generally.

Conclusion

There may be still a correlation between transitional cell carcinoma in UUT and the classic serum tumor markers like CA199□CA242□CA724 and CEA. Tumor metastasis may effect this phenomenon, and high pressure induced by hydronephrosis may be one reason of abnormal CSTMs changes. Hydronephrosis caused by UTUC was associated with poor prognosis and whether it may induced tumor metastasis need further study.

Abbreviations

UTUC: upper tract urothelial carcinoma; CSTM: classic serum tumor markers; TCC: transitional cell carcinoma; CA: cancer antigen; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; SCC-Ag: squamous cell carcinoma antigen; RCC: renal cell carcinoma; HL: hydrop length.

Declarations

Ethics approval and consent to participate

This research was approved by the Ethics Committee at the Shanghai Jiaotong University Medical School Affiliated Ruijin Hospital North. Informed consent was obtained from all individual participants included in this research. All procedures performed in this research involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was signed and obtained from all individual participants included in the study.

Consent for Publication

Not applicable.

Availability of data and material

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

No competing interests in this research.

Funding

This research was supported by the Research Program of Shanghai Jiaotong University Medical School Affiliated Ruijin Hospital North(No.2016ZY07) and the Research Program of Shanghai Science and Technology Commission (No. 19ZR1432300). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

JWP: Project development; XWJ: Manuscript writing; Data analysis; WCT: Data collection; XZ: Data collection; BXH: Data analysis; DWW: Patient follow-up; GLL: Data analysis; YZ: Literature research; BKL: Patient follow-up; XJW: Data collection; DX: advisor; XHW: advisor; YS: Research design and manuscript editing. All authors have read and approved the manuscript.

Acknowledgements

Not Applicable.

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Tables

Table 1 Rate of abnormal changes of CSTMs in UTUC, simple hydronephrosis with no carcinoma and renal cell carcinoma patients

	Rate of abnormal changes of CSTMs (%)	P value
UTUC (n=40)	52.50	
Non-tumoral hydronephrosis (n=37)	29.73	0.064, (0.036 one side)
Renal cell carcinoma (n=44)	27.27	0.025

Any one in 7 CSTMs showed an abnormal result was considered as positive; Chi-square test was used for comparison; All P values were calculated for each group compared to UTUC group.

Table 2 Ureteral TCC and simple hydronephrosis with no carcinoma

	Ureteral TCC (n=22)	Non-tumoral hydronephrosis (n=37)	P value
Status of hydrops of renal pelvis (mm)	32.160±15.449	76.595±41.359	<0.0001
Rate of abnormal changes of STMs (%)	68.182	29.730	0.006

Status of hydrops of renal pelvis was showed as the border diameter between extrarenal and intrarenal renal pelvis; For two groups, T test was used for analyzing status of hydrops of renal pelvis and chi-square test was used for analyzing rate of abnormal changes of STMs.

Table 3 Comparison of CSTMs changes in UTUC patients before and after surgery

	Pre-operative	Post-operative	P value
Number of abnormal CSTM changes (n=19)	1.00±0.88	0.53±0.77	0.02
Rate of abnormal CSTM changes (%)	63.16	36.84	0.19

T test was used for comparison for each two groups.

Table 4 UTUC metastasis and changes of CSTMs

	Normal CSTMs (item, %)	Abnormal CSTMs (item, %)	P value
Non-metastatic ureteral TCC (n = 17)	6 38.89	11 61.11	0.318
Non-metastatic renal pelvic TCC (n = 17)	10 58.82	7 41.18	
Metastatic ureteral TCC (n = 5)	0 0.00	5 100.00	/
Metastatic renal pelvic TCC (n = 1)	0 0.00	1 100.00	
Non-metastatic UTUC (n = 34)	16 48.57	18 51.43	0.06
Metastatic UTUC (n = 6)	0 0.00	6 100.00	(0.04, one side)

Metastatic UTUC included 5 patients with metastasis occurring at the first diagnosis and 1 patient with postoperative metastasis. Chi-square test was used for comparison for each two groups.

Table 5 Pathological manifestation and changes of CSTMs in on-metastasis UTUC patients

	Normal CSTMs	Abnormal CSTMs	P value
	(item, %)	[item, %]	
Low grade UTUC (n = 6)	0[0.00]	6[100.00]	0.02
High grade UTUC (n = 27)	15[55.56]	12[44.44]	
Non-infiltrating UTUC (n = 6)	0[0.00]	6[100.00]	0.02
Infiltrating UTUC (n = 27)	15[55.56]	12[44.44]	

Chi-square test was used for comparison for each two groups.

Table 6 Tumor load and the number of abnormal CSTM changes in non-metastatic UTUC

	Volume (mm ³)	Number of abnormal CSTM changes	P value
Tumor load	10198±11145	1.22±1.25	0.35

The liner regression analysis was used for comparison for each two groups.

Table 7 Correlation between hydronephrosis status and the number of abnormal CSTM changes in non-metastatic UTUC

	Hydrop length (LH, mm)	Number of abnormal CSTM changes	Regression formula	P value
Non-metastatic ureteral TCC (n = 18)	30.76 ± 15.00	1.17 ± 1.10	- 0.2369 + 0.0456 × HL	0.01
Non-metastatic renal pelvic TCC (n = 17)	15.23 ± 8.98	0.47 ± 0.62	-0.0837 + 0.0364 × HL	0.03
Non-metastatic ureteral UTUC (n = 35)	23.22 ± 14.58	0.83 ± 0.95	-0.1869 + 0.0437 ×HL	<0.0001

Hydrop length was measured by CT scan. The liner regression analysis was used for each group.

Table 8 Status of hydronephrosis between metastatic UTUC and non-metastatic UTUC

	Hydrop length (mm)	P value
Metastatic ureteral UTUC (n = 5)	32.91 ± 20.06	0.35
Non-metastatic ureteral UTUC (n = 35)	23.22 ± 14.58	

T test was used for comparison for each two groups.

Table 9 Status of hydrups in UUT and each CSTM

	CA199	CA242	CA724	CEA	SCC	CA125	AFP
Non-metastatic ureteral TCC [P value]	0.001	0.006	0.38	0.25	0.89	/	/
Non-metastatic renal pelvic TCC [P value]	0.83	0.92	0.0006	0.006	0.90	/	/
Non-metastatic UTUC (P value)	<0.0001	0.0001	0.04	0.85	0.44	/	/

The liner regression analysis was used for analyzing the hydronephrosis status and the number of abnormal CSTM changes in each group, P values were presented upon.

Figures

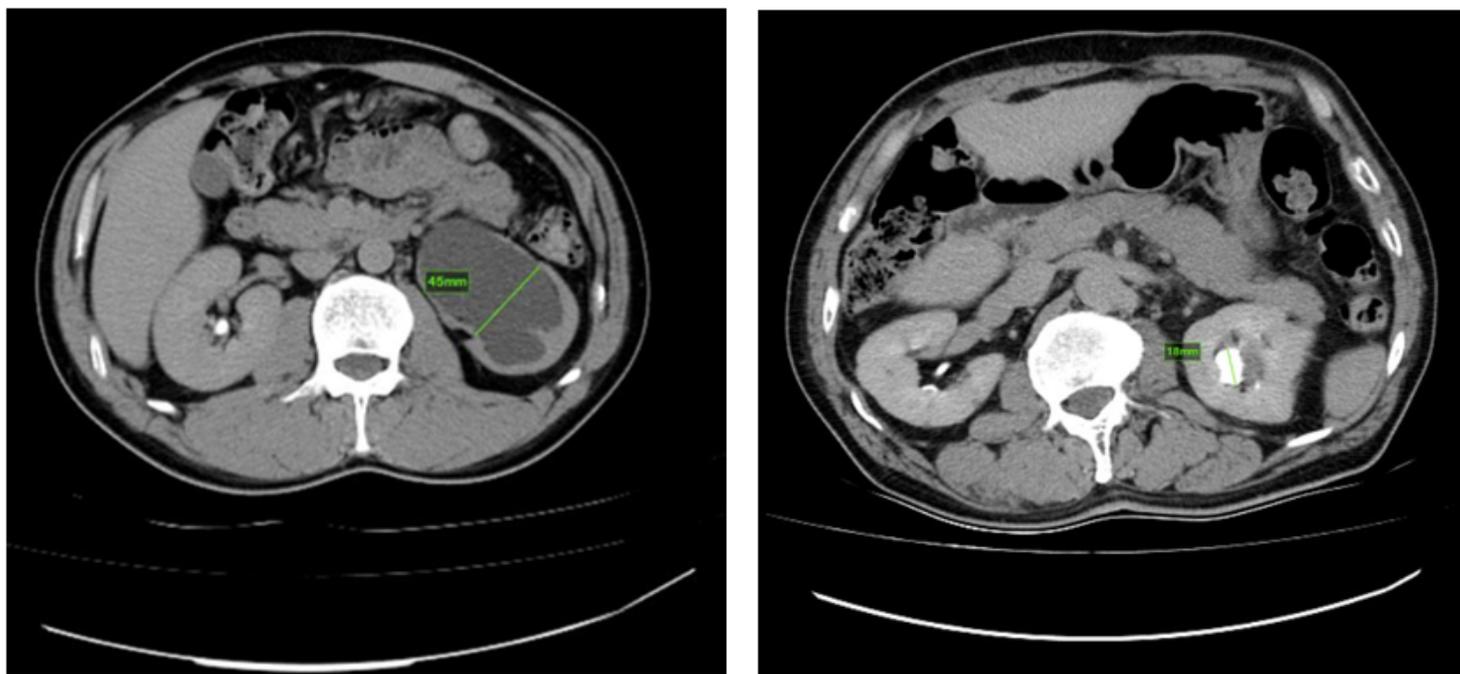


Figure 1

The dilation of hydronephrosis was assessed as hydrop length using the border diameter between extrarenal and intrarenal renal pelvis (for ureteral TCC, Left) or longest diameter of hydrop renal calyce (for renal pelvic TCC, Right) measured in kidney CT scanning.

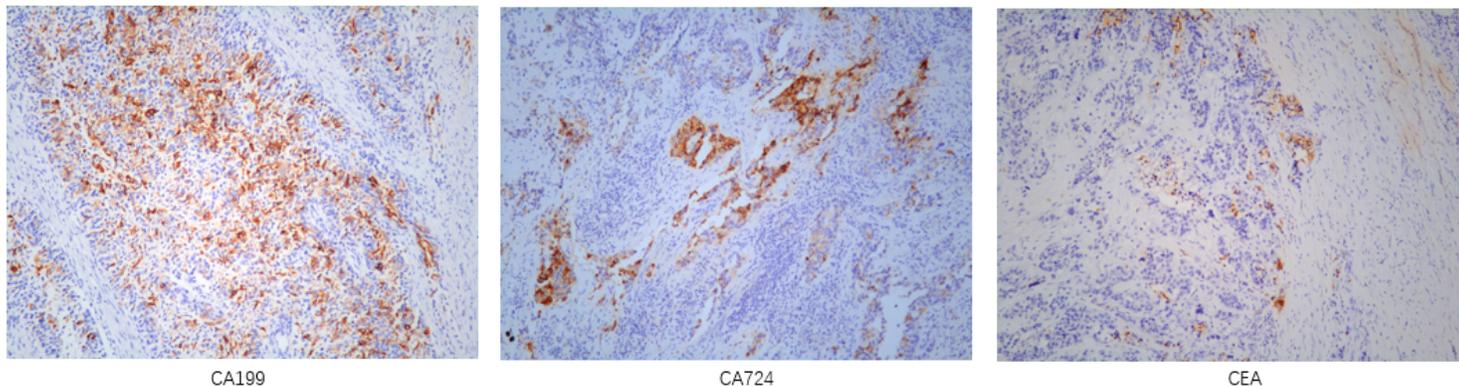


Figure 2

The expressions of CA199, CA724 and CEA in UTUC (at a magnification of $\times 100$). Immunohistochemistry technology was used to verified CA199, CA724 and CEA were common expressed in UTUC tissue.