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Original Article

Systemic inflammatory responses predict survival outcomes and male gender predicts metachronous bladder cancer of upper tract urothelial carcinoma

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Abstract: *Objective:* To investigate predictive markers for prognosis and intravesical recurrence in patients with upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU). *Material and methods:* We retrospectively studied 113 patients with UTUCs who underwent RNU between December 2005 and January 2015 at Huashan Hospital and analyzed their clinicopathological parameters. *Results:* The median follow-up was 29 months (range 2-113 months). Until October 2015, 82 patients (72.6%) were still alive and intravesical recurrence was observed in 22 patients (20%) at the last follow-up. Multivariate analysis showed that tumor stage, tumor size, lymphovascular invasion (LVI), derived neutrophil-lymphocyte ratio (dNLR), serum creatinine and serum albumin were independent predictors for cancer-specific survival. Gender and prophylactic intravesical chemotherapy were independently associated with intravesical recurrence-free survival. *Conclusion:* Systemic inflammatory responses, including blood dNLR and serum albumin, were potential prognostic factors for UTUC patients after RNU, which suggested that inflammatory response mechanisms played an important role in prognosis of patients with UTUC. Besides intravesical chemotherapy, male gender was an independent risk factor for metachronous bladder cancer for UTUC patients underwent RNU.

Keywords: Upper tract urothelial carcinoma, male gender, systemic inflammatory responses, creatinine, survival, intravesical recurrence

Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 5-10% of all urothelial carcinomas [1]. Unlike the natural history of bladder cancer, up to 60% of UTUCs are invasive, whereas only 15-20% of bladder tumors are invasive [2]. Radical nephroureterectomy (RNU) with bladder-cuff excision is the surgical standard of care for patients with non-metastatic UTUC. However, due to its aggressive nature, oncologic outcomes of UTUC patients after RNU remain relatively poor [3]. It has been reported that 5-year cancer-specific survival (CSS) is <50% for pT2-3 disease and <10% for pT4 disease [4]. Although tumor stage and grade are the most significant prognostic factors for UTUC [5], they are not enough to predict outcome. There is a need to identify new prognostic markers to provide additional prognostic information for patients with UTUC. Moreover, although local recurrence rate is rare after RNU, the intravesical recurrence rate ranges from 22% to 47% [6]. Therefore, regular follow-up for bladder recurrence is mandatory in UTUC patients after RNU. However, risk factors associated with intravesical recurrence after RNU remain controversial. In this study, we decided to investigate predictive markers for prognosis and intravesical recurrence in patients with UTUC after RNU.

Material and methods

We retrospectively studied 113 patients with UTUC who underwent surgery between December 2005 and January 2015 at Huashan Hospital. All patients were confirmed with urothelial malignancy pathologically. Any patients with distant metastatic UTUC were excluded

Table 1. Clinicopathologic characteristics of patients with upper tract urothelial carcinoma

Variables		n (%)
Age (years)		64.86±10.23
Gender	Female	37 (32.7%)
	Male	76 (67.3%)
Gross hematuria	Absent	27 (23.9%)
	Present	86 (76.1%)
BMI (kg/m^2)		23.42±3.24
Tumor grade	Low grade	37 (32.7%)
	High grade	76 (67.3%)
Tumor stage	Ta	50 (44.2%)
	T1	14 (12.4%)
	T2	17 (15.0%)
	T3-T4	32 (28.3%)
Lymph node metastasis	Absent	105 (92.9%)
	Present	8 (7.1%)
Tumor location	Renal pelvis	58 (51.3%)
	Ureter	45 (39.8%)
	Both	10 (8.8%)
Tumor number	Unifocal	98 (86.7%)
	Multifocal	15 (13.3%)
Tumor size	≤3 cm	68 (60.2%)
	>3 cm	45 (39.8%)
Concomitant bladder cancer	Absent	103 (91.2%)
	Present	10 (8.8%)
Lymphovascular invasion	Absent	92(81.4%)
	Present	21 (18.6%)
Non-functioning kidney	Absent	96 (85.0%)
	Present	17 (15.0%)
Derived neutrophil-lymphocyte ratio		5.94±1.91
Platelet-lymphocyte ratio		131.24±54.93
Serum urea (mmol/L)		6.45±2.10
Serum creatinine (μmol/L)		90.25±26.86
Serum albumin (g/L)		39.87±3.40
Serum prealbumin (g/L)		237.91±49.48

from the study. All specimens were acquired from radical nephroureterectomy (RNU) with bladder-cuff excision. All sections were reviewed independently by two pathologists without knowledge of patient profile. Lymph node dissection was performed when suspicious lymph nodes were discovered during the procedure. The tumors were graded according to the World Health Organization (WHO)/International Society of Urological Pathology (ISUP). The tumor stage was determined in accordance with the Union for International Cancer Control (UICC) 2009 TMN classification for urothelial carcinoma of the upper urinary tract. As for heterogeneity conditions, lesions that involved two grades or stages were classified according to the higher ones identified in the specimen. Tumor location was defined as renal pelvic, ureteral or both. Tumor multifocality was defined as the synchronous presence of ≥2 pathologically confirmed tumors in any location of upper urinary tract. Tumor size was defined as the largest diameter of the tumor in the specimen. Ipsilateral non-functioning kidney was defined as unilateral kidney glomerular filtration rate (GFR) below 10 ml/min, which was calculated by SPECT/CT, based on 99mTc-DTPA detection. All of the laboratory data were measured within 2 weeks preoperatively.

There were 67 patients with UTUC undergoing open RNU with bladder-cuff excision. Forty-two patients underwent laparoscopic RNU and bladder-cuff excision. There were 3 patients underwent transurethral resection of bladder tumor (TURBt) preoperatively due to concomitant non-muscle invasive bladder cancer (NMIBC). Four patients underwent RNU and radical cystectomy because of pathologically confirmed concomitant muscle invasive bladder cancer (MIBC). Adjuvant cisplatin-based systemic chemotherapy was routinely administrated in patients with pT3-T4 diseases postoperatively. Fifty patients (45.5%) received prophylactic intravesical chemotherapy postoperatively with pirarubicin postoperatively. The prophylactic intravesical instillation was accorded to the following regime: weekly administration for 8 weeks and followed by monthly administration for 6 to 10 months.

Patients were generally followed every 3 months for the first 2 years, every 6 months during the third through the fifth years, and annually thereafter. Follow-up consisted of routine physical examinations, blood tests, medical imaging examinations and cystoscopic evaluation. Cystoscopy was performed in bladder-preserved patients every 3 months during the first year, every 6 months during the second year and once a year from the third year onwards. All patients were followed retrospectively both through hospital records and by telephone interviews. Cause of death was deter-

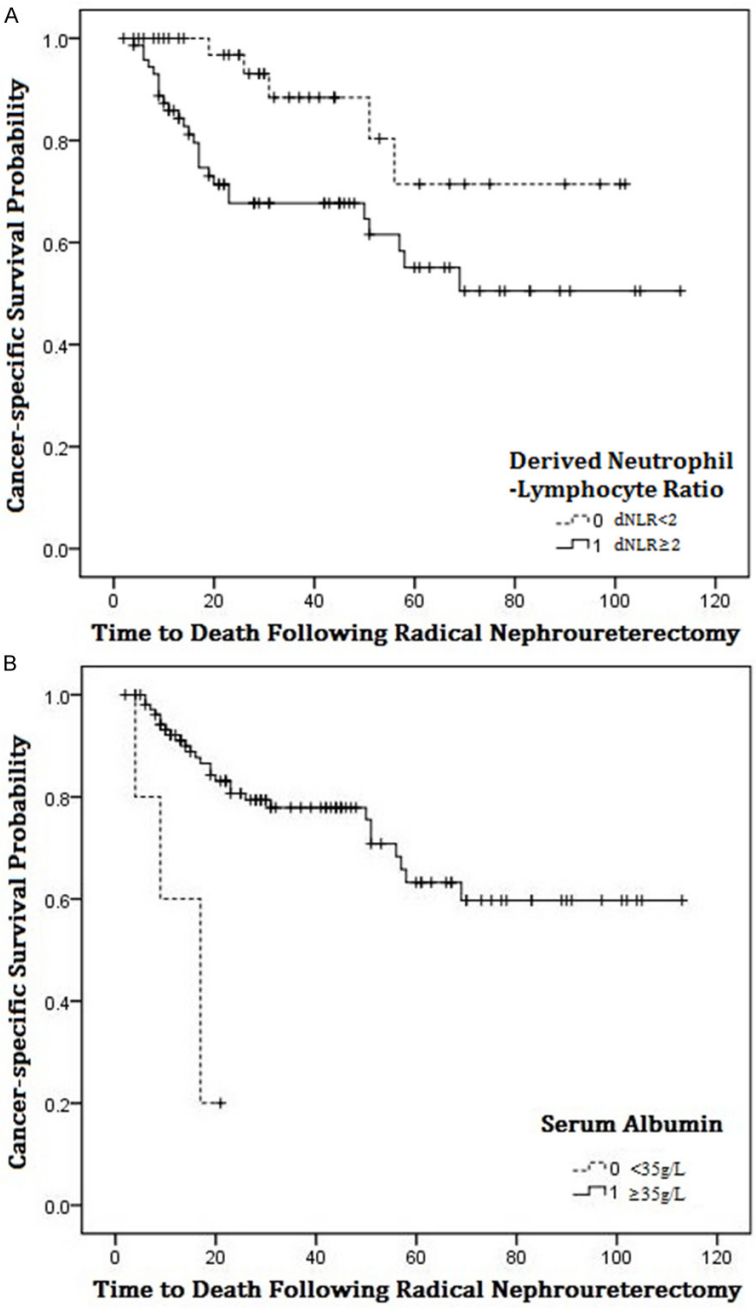

Figure 1. Cancer-specific survival probability of patients underwent radical nephroureterectomy for upper tract urothelial carcinoma based on (A) derived neutrophil-lymphocyte ratio; (B) serum albumin.

mined by treating physicians, by chart review and authorized death certificate. Perioperative mortality (death within 30 days after RNU) was censored at time of death for cancer-specific survival (CSS) analyses. Informed consents were obtained from all patients and the study was approved by the Huashan institutional review board (HIRB).

The SPSS 17.0 for Windows was used for statistical analyses. All data were presented as mean ± standard deviation (SD). Multivariate Cox proportional regression analyses were performed to determine the independent contribution of clinicopathological factors to CSS and intravesical recurrence-free survival (RFS). The end-point variables of interest were cancer specific deaths and intravesical tumor recurrences, respectively. These hazards were estimated with their 95% confidence interval. Statistical significant was set at $P<0.05$.

Results

Population characteristics

Patients' demographics and clinicopathological characteristics were listed in **Table 1**. There were 76 males (67.3%) and 37 females (32.7%). The mean age of the patients at the time of surgery was 64.86 (range 40-85) years. There were 58 patients (51.3%) with renal pelvic tumors, 45 patients (39.8%) with ureteral tumors and 10 patients (8.8%) with tumors in both. There were 15 patients (13.3%) with multifocal tumors of upper urinary tract whilst 10 patients (8.8%) with concomitant bladder cancer at diagnosis. The stage distribution of the patients was 44.2% pTa, 12.4% pT1, 15.0% pT2 and 28.3% pT3-4. Lymph node (LN) metastasis was noticed in 8 cases (7.1%). Tumor grade were distributed as low grade in 37 (32.7%) and high grade in 76 cases (67.3%).

Cancer-specific survival

The median follow-up was 29 months (range 2-113 months). As of October 2015, 82 pati-

Table 2. Cox regression in the prediction of cancer-specific survival of patients with upper tract urothelial carcinoma

		RR	95% CI	*P* value
Gender	(Female/Male)	0.501	0.185-1.356	0.174
Gross hematuria	(Absent/Present)	0.522	0.180-1.516	0.232
Body mass index				0.723
	<18.4	1	-	-
	18.5-24.9	2.522	0.248-25.643	0.434
	≥25.0	2.631	0.244-28.392	0.425
Tumor grade	(Low grade/High grade)	0.731	0.282-1.899	0.521
Tumor stage				0.008**
	Ta/T1	1	-	-
	T2	4.337	1.036-18.158	0.045
	T3-T4	0.384	0.104-1.413	0.150
Lymph node metastasis	(Absent/Present)	0.000	-	0.982
Tumor location				0.660
	Renal pelvic	1	-	-
	Ureter	1.641	0.534-5.045	1.641
	Ureter & Renal pelvic	1.186	0.053-26.560	0.914
Tumor number	(Unifocal/Multifocal)	1.455	0.140-15.135	0.753
Tumor size	(≤3 cm, >3 cm)	4.271	1.452-12.560	0.008**
Concomitant bladder cancer	(Absent/Present)	0.854	0.152-4.790	0.857
Lymphovascular invasion	(Absent/Present)	3.740	1.107-12.635	0.034*
Non-functioning kidney	(Absent/Present)	0.000	-	0.982
Derived eutrophil-lymphocyte ratio	(<2, ≥2)	5.147	1.390-19.066	0.014*
Platelet-lymphocyte ratio	(<150, ≥150)	1.858	0.677-5.100	0.229
Serum urea	(<7 mmol/L, ≥7 mmol/L)	0.500	0.108-2.318	0.376
Serum creatinine	(<130 μmol/L, ≥130 μmol/L)	4.003	1.182-13.552	0.026*
Serum albumin	(<35 g/L, ≥35 g/L)	0.112	0.032-0.552	0.007**
Serum prealbumin	(<280 g/L, ≥280 g/L)	0.653	0.199-2.145	0.482

**Correlation is significant at the 0.01 level (two-tailed). *Correlation is significant at the 0.05 level (two-tailed).

ents (72.6%) were still alive at the last follow-up. Thirty-one patients (27.4%) died of UTUC during follow-up. Multivariate analysis showed that tumor stage (P=0.008), tumor size (≤3 cm *vs.* >3 cm, RR=4.271, 95% CI=1.452-12.560, P=0.008), lymphovascular invasion (LVI) (absent *vs.* present, RR=3.740, 95% CI=1.107-12.635, P=0.034), serum creatinine (<1.4 mg/dL *vs.* ≥1.4 mg/dL, RR=4.003, 95% CI=1.182-13.552, P=0.026), derived neutrophil-lymphocyte ratio (dNLR) (<2 *vs.* ≥2, RR=5.147, 95% CI=1.390-19.066, P=0.014) (**Figure 1A**) and serum albumin (<35 g/L *vs.* ≥35 g/L, RR=0.112, 95% CI=0.032-0.552, P=0.007) (**Figure 1B**) were independent predictors for CSS (**Table 2**).

Metachronous bladder cancer

Follow-up data from 110 patients with UTUC undergoing RNU were involved, 3 cases were excluded because of synchronous cystectomy. Until October 2015, intravesical recurrence of bladder cancer occurred in 22 patients (20%) at the last follow-up. Seventeen patients (77.3%) with metachronous bladder cancer were NMIBC whereas 5 of them were MIBC. In multivariate analysis, both gender (female *vs.* male, RR=4.170, 95% CI=1.036-16.781, P=0.044) (**Figure 2**) and prophylactic intravesical chemotherapy (no *vs.* yes, RR=0.237, 95% CI=0.065-0.870, P=0.030) were independently associated with intravesical RFS (**Table 3**).

Discussion

Pathologic tumor stage represents the best-established predictor of survival in patients with UTUC. Several population-based studies have confirmed the prognostic value of pathologic stage. The 5-year CSS in patients with pTa/T1 diseases was >90% and it decrease to

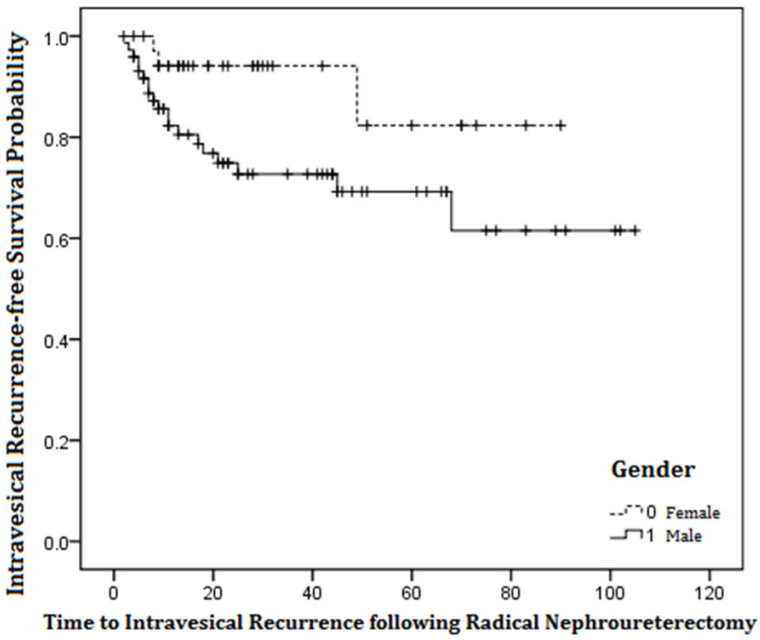

Figure 2. Intravesical recurrence-free survival probability of patients underwent radical nephroureretectomy for upper urinary tract urothelial carcinoma based on gender.

<20% in patients with pT4 disease [2, 7-10]. About 20%-40% of UTUC patients harbor lymph node metastases, which largely depends on the pT stage [11]. Several studies demonstrated the prognostic value of lymph node metastases [2, 9], and LVI was proved as an independent predictor of survival [12]. Several studies also validated a powerful prognostic role of tumor grade [13], but this was not confirmed in the multivariate analyses of another study because of the strong correlation between tumor stages and grades [14]. Tumor initial location within the upper urinary tract and tumor multifocality were both proved to have independent prognostic effect in patients with UTUC [15]. Tumor size is also an established predictor of cancer-related outcomes in UTUC patients. In the study of Simone *et al* [16], no metastases were observed in patients with a tumor size <3 cm, and patients with a tumor size ≥3 cm had a 5-year metastasis-free survival of 67%. In our cohort, tumor pT stage, LVI and tumor size were independently correlated with CSS while the significant prognostic value of tumor grade, lymph node metastasis, tumor location and multifocality were not observed, which suggests that the former prognostic factors could be more meaningful.

Chronic inflammation plays an important role in cancer development and progression [17]. The host systemic inflammatory response can be assessed by examining acute-phase protein levels including albumin. Albumin was no longer considered as a nutritional marker, but rather an inflammatory response marker. Chronic malnutrition and chronic inflammatory reaction caused by cancer eventually lead to hypoalbuminemia [18]. Hypoalbuminemia has been proved to provide additional prognostic value in various cancers. Gregg *et al* [19] reported that hypoalbuminemia is predictive of increased 90-day mortality and poor overall survival after radical cystectomy for baldder cancer. In UTUC patients, Ku *et al* [20] reported that pretreatment serum albumin was significantly associated with disease-specific survival, and had prognostic value independent of TNM stage. In our series, serum albumin was an independent prognostic factor for CSS. In addition, serum prealbumin level, which was considered to be a potential nutritional marker [21], did not have prognostic effect on UTUC patients.

Cellular components of systemic inflammatory response, including neutrophils, lymphocytes and platelets, also have been proved to have prognostic values in patients with various cancers. Gondo *et al* [22] indicated that neutrophil-lymphocyte ratio (NLR) was an independent prognostic factor in bladder cancer patients after radical cystectomy. Proctor *et al* [23] suggested that dNLR (nuetrophil count/white cell count-neutrophil count) as another independent prognostic factor in patients with cancer. Kim *et al* [24] first reported that dNLR was a marker for predicting disease-specific survival for 5 years after curative RNU. Zhang *et al* [25] reported that platelet-lymphocyte ratio (PLR) was correlated with overall survival in univariate analysis but failed to prove its independent prognostic value in multivariate analysis in patients with advanced bladder cancer. In our

Table 3. Cox regression in the prediction of intravesical cancer recurrence-free survival of patients with upper tract urothelial carcinoma

		RR	95% CI	*P* value
Gender	(Female/Male)	4.170	1.036-16.781	0.044*
Gross hematuria	(Absent/Present)	1.242	0.363-4.250	0.730
Body mass index				0.788
	<18.4	1	-	-
	18.5-24.9	6.572E4	0.000-6.75E122	0.936
	≥25.0	4.465E4	0.000-4.59E122	0.938
Bladder cancer history	(Absent/Present)	0.420	0.033-5.412	0.506
Tumor grade	(Low grade/High grade)	1.841	0.449-7.546	0.397
Tumor stage				0.305
	Ta/T1	1	-	-
	T2	0.650	0.152-2.780	0.562
	T3-T4	0.275	0.053-1.420	0.123
Lymph node metastasis	(Absent/Present)	1.001	0.071-14.130	0.999
Tumor location				0.940
	Renal pelvic	1	-	-
	Ureter	0.797	0.218-2.917	0.732
	Ureter & Renal pelvic	0.000	0.000-2.15E107	0.930
Tumor number	(Unifocal/Multifocal)	5.114	0.340-76.927	0.238
Tumor size	(≤3 cm, >3 cm)	0.731	0.211-2.538	0.622
Concomitant bladder cancer	(Absent/Present)	1.016	0.175-5.890	0.985
Non-functioning kidney	(Absent/Present)	1.136	0.256-5.042	0.867
Derived neutrophil-lymphocyte ratio	(<2, ≥2)	0.601	0.174-2.080	0.422
Platelet-lymphocyte ratio	(<150, ≥150)	1.419	0.439-4.582	0.559
Serum urea	(<7 mmol/L, ≥7 mmol/L)	2.316	0.513-10.449	0.275
Serum creatinine	(<130 μmol/L, ≥130 μmol/L)	1.507	0.406-5.593	0.540
Serum albumin	(≥35 g/L, <35 g/L)	0.209	0.024-1.780	0.152
Serum prealbumin	(≥280 g/L, <280 g/L)	1.095	0.281-4.260	0.896
Intravesical chemotherapy	(No/Yes)	0.237	0.065-0.870	0.030*

*Correlation is significant at the 0.05 level (two-tailed).

cohort, dNLR negatively correlated with CSS in UTUC patients, while significant prognostic effect of PLR was not observed.

The pathogenesis of metachronous bladder cancer after RNU for UTUC is still unclear. Metachronous bladder cancer might result from either intraluminal seeding and implantation of cancer cells or field cancerization. Several studies recently suggested that both mechanisms might be involved in the development of metachronous bladder cancer [26]. In most studies, there showed no significant difference in the risk of metachronous bladder cancer between males and females with UTUC [10, 27-29]. In our series, however, male gender was independently correlated with intravesical RFS in multivariate analysis. Since bladder cancer in men have a higher incidence and showed more aggressive and invasive potential than women [30, 31], that could partly explain the gender gap in UTUC patients. Nevertheless, the difference in biological characteristics of UTUC cells between male and female remains further exploration.

The rate of intravesical recurrence following RNU for UTUC was frequent, predominantly in the first 2 years after RNU [26]. In a meta-analysis by Fang *et al* [32], postoperative intravesical chemotherapy significantly decreases the risk of intravesical recurrence after RNU for UTUC patients. In our series, prophylactic intravesical chemotherapy negatively correlated with intravesical RFS. In addition, other previously reported predictors of postoperative in-

travesical recurrence, including ipsilateral hydronephrosis, bladder cancer history, tumor location, tumor size, tumor multifocality, tumor stage and grade showed no independent predictive effect on intravesical RFS in our study.

To conclude, our study demonstrated that systemic inflammatory responses, including blood dNLR and serum albumin, are potential prognostic factors for UTUC patients after RNU, which suggested that inflammatory response mechanisms played an important role in prognosis of patients with UTUC. Besides intravesical chemotherapy, male gender was an independent risk factor for metachronous bladder cancer for UTUC patients underwent RNU.

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Disclosure of conflict of interest

None.

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