



Prognostic Impact of Preoperative Anemia on Urothelial and Extraurothelial Recurrence in Patients With Upper Tract Urothelial Carcinoma

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Abstract

We examined the effect of preoperative anemia on urothelial and extraurothelial recurrence (EUR) after radical nephroureterectomy. Anemia is the most common and most persistent hematologic abnormality faced by cancer patients. Patients with preoperative anemia had a greater probability of having upper tract urothelial carcinoma with higher tumor stages, higher tumor grades, and lymph node metastasis. Anemia was also an independent predictor of EUR.

Background: To investigate the prognostic impact of preoperative anemia on urothelial and extraurothelial recurrence after radical nephroureterectomy. **Methods:** A single-center series of 238 consecutive patients who were treated with radical nephroureterectomy for upper tract urothelial carcinoma was evaluated. We categorized patients on the basis of hemoglobin level into 2 groups, including normal or anemia. Survival was estimated using the Kaplan-Meier method. Cox proportional hazard regression models were used to evaluate the association of preoperative anemia with outcome, controlling for clinicopathologic variables. **Results:** Ninety-seven patients (40.8%) had anemia (median hemoglobin level, 143 vs. 107 g/L). Preoperative anemia was associated with history of bladder cancer ($P = .01$), tumor multifocality ($P = .03$), lymphovascular invasion ($P = .05$), and adjuvant chemotherapy ($P = .01$). Higher tumor stage and grade, and lymph node metastasis were significantly associated with preoperative anemia. Preoperative anemia was independently associated with extraurothelial recurrence (hazard ratio, 1.95; 95% confidence interval, 1.14-3.34; $P = .01$) in multivariate Cox regression analyses. Only a history of bladder tumor (hazard ratio, 2.07; $P = .009$) and tumor multifocality (hazard ratio, 3.97; 95% confidence interval, 2.37-6.67; $P < .001$) were independently associated with urothelial recurrence. The 5-year cancer-specific survival for patients with normal hemoglobin level was 82.1% and for patients with preoperative anemia was 54.2%. **Conclusion:** Patients with preoperative anemia had a greater probability of having upper tract urothelial carcinoma with higher tumor stages, higher tumor grades, and lymph node metastasis (pN+). Preoperative anemia was statistically significantly associated with worse cancer-specific survival and extraurothelial recurrence in patients who underwent radical nephroureterectomy.

Clinical Genitourinary Cancer, Vol. 13, No. 5, 485-91 © 2015 Elsevier Inc. All rights reserved.

Keywords: Anemia, Radical nephroureterectomy, Recurrence, Survival, Upper urinary tract urothelial carcinoma

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Submitted: Jan 25, 2015; Revised: Mar 20, 2015; Accepted: Mar 22, 2015; Epub: Mar 30, 2015

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Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon disease, accounting for 5% of all urothelial carcinomas with an incidence of 2 cases per 100,000 person-years.¹ These tumors often behave aggressively, with reported recurrence rates of 22% to 66%.^{2,3} Because the disease recurrence and progression rates are high in patients with UTUC,² an improved understanding of the prognostic parameters may lead to the identification of patients who may benefit from intensified therapy and monitoring.

Pathologic T stage, lymphovascular invasion (LVI), and C-reactive protein levels are documented as major prognostic factors for

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recurrence of UTUC.⁴⁻⁶ Few studies have been performed to identify the preoperative predictors of UTUC recurrence.⁷⁻⁹ Hashimoto et al reported that cT stage and a neutrophil counts of $\geq 4000/\mu\text{L}$ were independent predictors of recurrence.⁷ Brien et al reported that the presence of hydronephrosis, ureteroscopic grade, and cytology may identify UTUC patients at risk for muscle-invasive disease.⁸

Recently Rink et al reported that preoperative anemia was an independent predictor of disease recurrence and cancer-specific mortality.⁹ The hemoglobin level fulfills several features of an optimal biomarker.¹⁰ It is easily accessible, inexpensive to test, and used in daily clinical practice. However, because of the rarity of the disease, the significance of preoperative anemia has not been clearly established in UTUC.

The present study aimed to identify the prognostic impact of preoperative anemia on urothelial and extraurothelial recurrence (EUR) after radical nephroureterectomy (RNU) in patients with UTUC.

Patients and Methods

Patient Selection

The present study cohort represents 307 patients who were surgically treated for UTUC with nephroureterectomy between January 1999 and December 2013. Patients who had a history of bladder tumor at a higher stage than the upper tract disease, preoperative chemotherapy, or previous contralateral UTUC were excluded. None of the patients included in this study had distant metastasis at diagnosis of UTUC. Patients with concomitant bladder cancer and those with gross hematuria were also excluded (18 patients). No patient received hematopoiesis inducing drugs. In total, 238 patients (mean age, 66.5 years; range, 36 to 88 years) were then available for evaluation.

Because previous reports challenged the World Health Organization classification of anemia, we performed sensitivity analysis to consider patient age and gender.^{10,11} We categorized patients on the basis of hemoglobin level into 2 groups, including normal or anemia. Anemia was defined in male patients younger than 60 years as 13.7 g/dL or less and in those 60 years old or older as 13.2 g/dL or less.¹¹ In female patients of all ages, the corresponding threshold for anemia was 12.2 g/dL or less.¹¹ Regular blood evaluation, including hemoglobin measurement, was done on the first day of patient hospitalization, generally 1 to 7 days before RNU. Hemoglobin also was measured at least once within 3 days postoperatively.

The diagnosis of UTUC was established by computed tomography, excretory urography, a retrograde ureteropyelogram, and/or ureteroscopy with tissue biopsies. The initial treatment of all patients was open RNU. Lymph node dissection (LND) was performed in 49 patients, while 189 patients did not receive LND (pNx). Whether LND would be performed or not as well as the extent of LND when performed were determined by each surgeon and not by strict prospective criteria. The extent of LND ranged from just the ipsilateral hilar lymph nodes (LNs) to all LNs around the ipsilateral great vessels with or without interaortocaval LNs.

Pathologic Evaluation

Tumors were staged according to the tumor, node, metastasis classification system¹² and graded using the 1998 World Health Organization classification.¹³ Tumor location was defined as either

renal pelvic or ureteral on the basis of the location of the dominant tumor. The dominant lesion was defined as that with the highest pathologic tumor stage (pT). For multifocal tumors at the same stage, the higher grade was selected for main tumor location. Tumor multifocality was defined as the synchronous presence of 2 or more pathologically confirmed tumors in any upper urinary tract location. No immunohistochemistry techniques were used to determine the presence of LVI.

Follow-Up Regimen

Local recurrence and metastasis were considered to be EUR. Intravesical recurrence and recurrence in the contralateral UTUC were considered to be urothelial recurrence in this study. There were 4 patients with recurrence in the contralateral UTUC (ureter, $n = 2$; renal pelvis, $n = 2$). Routine follow-up consisted of physical examination and cystoscopy every 3 months during the first year and every 6 to 12 months thereafter. Chest radiography, abdominal ultrasonography, computed tomography, and excretory urography were performed annually, depending on the clinical stage of the cancer in the upper urinary tract. Most patients who were identified as having died from UTUC had progressive, widely disseminated metastases at the time of death. Cisplatin-based adjuvant chemotherapy was administered to some patients with pathologically confirmed lymph node metastasis (LNM) or with muscle-invasive disease (48 patients).

Statistical Analysis

Demographic and clinicopathologic factors were analyzed using the chi-square test or an unpaired t test. Recurrence-free probabilities and cancer-specific survival (CSS) were estimated by the Kaplan-Meier method, and the log-rank test was used for the statistical differences. We defined the time of surgery as time 0. Univariate and multivariate Cox proportional hazard regression models were used to evaluate the association between various clinicopathologic factors and urothelial recurrence, EUR, and cancer-specific mortality after surgery. Only the significant factors were entered into multivariate Cox proportional hazard regression models. In all tests, $P < .05$ (2 sided) was considered statistically significant.

Results

The patients' clinical and pathologic profiles are listed in Table 1. The median follow-up after surgery was 34.5 months (range, 1-154 months). One hundred forty-one patients (59.2%) had normal hemoglobin and 97 (40.8%) had anemia (median, 143 vs. 107 g/L).

Preoperative anemia was associated with history of bladder cancer ($P = .01$), tumor multifocality ($P = .03$), LVI ($P = .05$), and adjuvant chemotherapy ($P = .01$). Higher tumor stage and grade, and LNM were significantly associated with preoperative anemia (Table 1). Specifically, patients with preoperative anemia had a greater probability (55.9% vs. 17.9%) of having higher tumor stages (pT3 or greater).

Of the 238 patients included in the present study, 76 (31.9%) had urothelial recurrence and 65 (27.3%) had EUR. From the patients with EUR, 58.3% had initial recurrence in LNs, 35.5% had recurrence in distant organs, and 6.2% had recurrence in a local area. The median time to urothelial recurrence was 16.9 months

Table 1 Demographic, Clinical and Pathologic Profiles of 238 Patients With UTUC Managed by RNU, Stratified by Preoperative Hemoglobin Level

Variable	All	Normal Hemoglobin Level	Anemia	Chi-Square Score	P ^a
All	238 (100)	141 (59.2)	97 (40.8)	—	—
Age (years)	66.5 ± 8.9	66.1 ± 9.1	66.9 ± 8.7	—	.25 ^b
Sex				0.72	.39
Male	132 (55.4)	75 (56.8)	57 (43.2)		
Female	106 (44.6)	66 (62.3)	40 (37.7)		
Preoperative Hydronephrosis				1.6	.21
Absent	144 (60.5)	92 (64.2)	52 (35.8)		
Present	94 (39.5)	52 (55.8)	42 (44.2)		
History of Bladder Cancer				6.60	.010
Yes	58 (24.4)	26 (44.8)	32 (55.2)		
No	180 (75.6)	115 (63.8)	65 (36.2)		
Tumor Location				1.23	.26
Renal pelvis	142 (59.6)	80 (56.3)	62 (43.7)		
Ureter	96 (40.4)	61 (63.5)	35 (36.5)		
Tumor Focality				4.61	.03
Unifocal	161 (67.6)	103 (63.9)	58 (36.1)		
Multifocal	77 (32.4)	38 (49.3)	39 (50.7)		
Tumor Size				2.05	.15
≤3 cm	99 (41.6)	64 (64.6)	35 (35.4)		
>3 cm	139 (58.4)	77 (55.4)	62 (44.6)		
Tumor Grade				23.24	.001
G1	24 (10.1)	22 (91.6)	2 (8.4)		
G2	95 (39.9)	65 (68.4)	30 (31.6)		
G3	119 (50.0)	54 (45.4)	65 (54.6)		
Tumor Stage				34.23	.001
pT2 or less	95 (39.9)	78 (82.1)	17 (17.9)		
pT3 or greater	143 (60.1)	63 (44.1)	80 (55.9)		
Lymph Node Metastasis				11.12	.004
pNx	189 (79.4)	118 (62.4)	71 (37.6)		
pN0	36 (15.1)	21 (58.3)	15 (41.7)		
pN+	13 (5.5)	2 (15.4)	11 (84.6)		
Lymphovascular Invasion				3.99	.046
Absent	84 (35.3)	57 (67.8)	27 (32.2)		
Present	154 (64.7)	84 (54.5)	70 (45.5)		
Adjuvant Chemotherapy				5.98	.014
Yes	48 (20.1)	21 (43.7)	27 (56.3)		
No	190 (79.9)	120 (63.2)	70 (36.8)		

Data are presented as n (%) or mean ± SD.

Abbreviations: RNU = radical nephroureterectomy; UTUC = upper tract urothelial carcinoma.

^aP value for χ^2 test unless indicated otherwise.

^bP value for unpaired *t* test.

(range, 3-85 months) and for EUR was 17.6 months (range, 3-73 months). EUR developed in 17.7% of patients with normal hemoglobin levels, whereas it occurred in 41.2% of those with preoperative anemia, which was statistically significant ($P < .001$).

By univariate analyses, history of bladder tumor (hazard ratio [HR], 3.96; 95% confidence interval [CI], 2.45-6.38; $P = .001$) and tumor multifocality (HR, 5.28; 95% CI, 3.29-8.47; $P < .001$) were associated with urothelial recurrence. By multivariate analysis, only history of bladder tumor (HR, 2.07; 95% CI, 1.20-3.58;

$P = .009$) and tumor multifocality (HR, 3.97; 95% CI, 2.37-6.67; $P < .001$) were associated with urothelial recurrence. Preoperative anemia was not associated with urothelial recurrence (HR, 1.43; 95% CI, 0.88-2.29; $P = .14$) (Table 2).

By univariate Cox regression analyses, preoperative anemia (HR, 4.02; 95% CI, 2.38-6.77; $P = .001$), tumor grade (HR, 2.03; 95% CI, 1.21-3.42; $P = .008$), tumor stage (HR, 22.6; 95% CI, 7.01-72.7; $P = .001$), LN status (HR, 4.12; 95% CI, 1.93-8.81; $P = .001$), LVI (HR, 1.85; 95% CI, 1.05-3.25; $P = .03$), and

Table 2 Univariate and Multivariate Cox Regression Models Predicting Urothelial and Extraurothelial Recurrence in 238 Patients After Radical Nephroureterectomy for UTUC

Variable	Urothelial Recurrence						Extraurothelial Recurrence					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Sex (male vs. female)	1.21	0.76-1.88	.43				0.84	0.51-1.37	.48			
Age (≤ 60 years vs. > 60 years)	0.84	0.51-1.39	.50				1.65	0.86-3.16	.13			
Anemia (no vs. yes)	1.43	0.88-2.29	.14				4.02	2.38-6.77	.001	1.95	1.14-3.34	.01
History of BC (no vs. yes)	3.96	2.45-6.38	.001	2.07	1.20-3.58	.009	1.54	0.91-2.61	.11			
Renal pelvis versus ureter	1.24	0.79-1.96	.34				0.75	0.45-1.25	.26			
Unifocal versus multifocal	5.28	3.29-8.47	.001	3.97	2.37-6.67	.001	1.12	0.67-1.87	.67			
Tumor size (≤ 3 cm vs. > 3 cm)	0.72	0.46-1.13	.15				1.32	0.80-2.18	.27			
G1 or G2 versus G3	0.79	0.51-1.25	.32				2.03	1.21-3.42	.008	0.73	0.41-1.28	.27
$\leq pT2$ versus $\geq pT3$	1.20	0.75-1.91	.44				22.6	7.01-72.7	.001	28.5	8.08-100.9	.001
pNx versus pN0	1.13	0.59-2.15	.72				1.38	0.72-2.68	.33			
pNx versus pN+	3.60	1.53-8.46	.003	1.58	0.65-3.86	.31	4.12	1.93-8.81	.001	2.12	0.96-4.62	.06
LVI (absent vs. present)	1.10	0.68-1.76	.69				1.85	1.05-3.25	.03	0.58	0.32-1.07	.08
Chemotherapy (no vs. yes)	1.12	0.64-1.97	.68				2.24	1.33-3.76	.02	1.80	1.04-3.12	.04

P values are for log-rank test.

Abbreviations: BC = bladder cancer; CI = confidence interval; HR = hazard ratio; LVI = lymphovascular invasion.

adjuvant chemotherapy (HR, 2.24; 95% CI, 1.33-3.76; $P = .02$) were associated with EUR. Preoperative anemia was independently associated with EUR (HR, 1.95; 95% CI, 1.14-3.34; $P = .01$) in multivariate Cox regression analyses (Table 2).

Urothelial recurrence-free survival after surgery for UTUC is not related to preoperative anemia ($P = .14$, log rank). However, EUR-free survival in patients with preoperative anemia was significantly lower compared with those with normal hemoglobin level ($P < .001$, log rank, mean EUR-free survival for patients with preoperative anemia 49.2 ± 9.3 months vs. mean EUR-free survival for patients with normal hemoglobin level 120.8 ± 6.1 months) (Figure 1).

The 5-year CSS estimate was 71%. However, in patients with EUR, the 5-year CSS estimate was 29.2%. In multivariate Cox regression analyses, preoperative anemia (HR, 2.67; 95% CI, 1.58-4.53; $P < .001$), tumor stage (HR, 18.6; 95% CI, 6.53-52.8; $P < .001$), and LN status (HR, 4.1; 95% CI, 1.97-8.72; $P = .001$) were the only independent predictors associated with worse CSS. The CSS in patients with preoperative anemia was significantly lower compared to those without preoperative anemia ($P < .001$, log rank, mean CSS for patients with preoperative anemia 48.5 ± 7.8 months vs. mean CSS for patients with normal hemoglobin level 111.1 ± 7.5 months) (Figure 2).

A total of 52 patients received perioperative blood transfusions. Perioperative blood transfusion was significantly associated with preoperative anemia ($P = .02$).

Discussion

Anemia is the most common and most persistent hematologic abnormality faced by cancer patients.¹⁴ Over the last decade,

Figure 1 Kaplan-Meier Estimates for Extraurothelial Recurrence-Free Survival Stratified According to Preoperative Hemoglobin Level in 238 Patients After RNU for UTUC

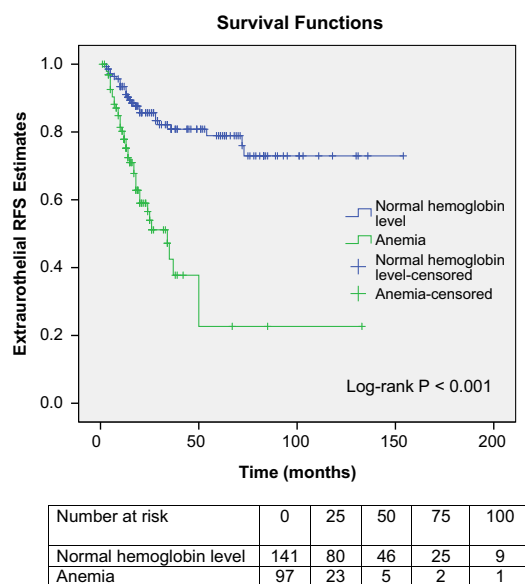
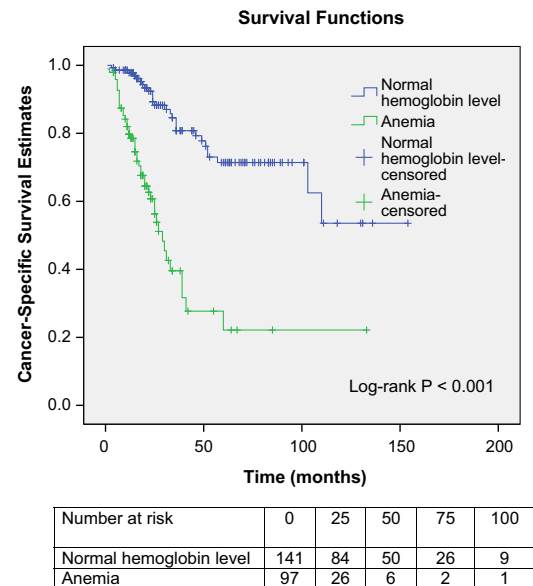


Figure 2 Kaplan-Meier Estimates for CSS Stratified According to Preoperative Hemoglobin Level in 238 Patients After RNU for UTUC



accumulating evidence has indicated that anemia is correlated with poor clinical outcome. Although some evidence suggests that hypoxia within the tumor microenvironment may lead to cellular quiescence, differentiation, and apoptosis, most evidence suggests that hypoxia in the tumor microenvironment provides selective pressure for the clonal expansion of cells that have acquired mutations.^{15,16} These mutations may result in increased treatment resistance, increased metastatic potential, and decreased cellular response to apoptosis signals.¹⁷

Recently, preoperative standard laboratory values such as hemoglobin, thrombocyte, and C-reactive protein were investigated as predictive factors in patients with bladder cancer and urothelial carcinoma of the upper urinary tract treated with extirpative surgery with curative intent.¹⁸ Rink et al demonstrated that preoperative anemia was a strong predictor of disease recurrence and cancer-specific mortality in patients treated with RNU for UTUC.⁹

In the present study, preoperative anemia was associated with history of bladder cancer, tumor multifocality, LVI, and adjuvant chemotherapy. Tumor multifocality is an independent prognosticator of disease progression and cancer-specific mortality in patients with organ-confined UTUC treated with RNU.¹⁹ Patients with preoperative anemia had a greater probability of having higher tumor stages (pT3 or greater). We also found that anemia was associated with higher tumor grades. In this study, patients with preoperative anemia had a greater probability (84.6% vs. 41.7%) of having LNM (pN+). More aggressive biological potential of tumors in patients with preoperative anemia could be a potential reason for a worse prognosis in these patients. Pathologic stage, LNM, and tumor grade have been

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established as prognostic factors for UTUC,^{2,3,20,21} and these features may be exacerbated by anemia. Furthermore, hypoxia may induce angiogenesis, which in turn can result in a higher proliferation rate for tumor cells.²²

The presence of hydronephrosis has been associated with more advanced disease stage^{23,24} and CSS.²⁵ It has been shown that anemia is not associated with preoperative hydronephrosis in patients with UTUC.⁹ This is in accordance with our results: 44.2% of patients with anemia had preoperative hydronephrosis, which was not statistically significant ($P = .21$).

In this cohort, cisplatin-based adjuvant chemotherapy was administered to some patients with pathologically confirmed LNM or with muscle-invasive disease (48 patients). It is estimated that only 20% of patients have a glomerular filtration rate of greater than 60 mL/min after nephroureterectomy.^{26,27} As a result, the published experience with adjuvant cisplatin-based chemotherapy has been limited to retrospective studies. The use of adjuvant chemotherapy in the treatment of UTUC remains largely limited because of the decline in renal function after RNU. The potential benefits of neoadjuvant chemotherapy in patients with UTUC include the treatment of early microscopic metastases and the ability to administer full-dose cisplatin with curative intent when both kidneys are still present.

In the present study, we noted that preoperative anemia is an independent predictor of EUR but had no effect on urothelial recurrence after RNU. Identification of preoperative predictors of EUR can aid in the decision making for LND. Currently, there is no consensus regarding the indications for LND at RNU for UTUC. LND may be omitted for low-risk patients. Omission of LND can decrease surgical invasiveness in those select patients. In addition, if high-risk patients can be identified on the basis of these predictors, the candidates for neoadjuvant chemotherapy can be selected. Ito et al noted that positive cytology, cT stage ≥ 3 , length of ureteral cancer ≥ 3 , and estimated glomerular filtration rate < 60 were preoperative predictive factors of EUR in patients with UTUC.²⁸

We found that perioperative blood transfusion was significantly associated with preoperative anemia. Linder et al noted that patients who received a perioperative blood transfusion were 31% more likely to die from bladder cancer than patients who did not receive a perioperative blood transfusion; receipt of a perioperative blood transfusion was likewise associated with increased risks of tumor recurrence and all-cause mortality.²⁹

The 5-year CSS for patients with normal hemoglobin level was 82.1% and for patients with preoperative anemia was 54.2%, which was statistically significant. In this study, preoperative anemia was identified as a significant predictor of cancer-specific mortality in patients treated surgically for UTUC. In accordance with previous studies, we also found that pathologic stage and LNM are independent predictors of survival in UTUC cases.^{2,20,21}

There are several limitations to the current study. First, it is inherently limited by biases associated with its retrospective design. We could not obtain complete information about perioperative blood transfusion; these data were not available for all patients, and therefore our analysis remained unadjusted for them. To eliminate common confounders that may be associated with bone marrow suppression, we excluded patients with preoperative systemic

chemotherapy from the study.³⁰ We also excluded patients with gross hematuria and those with concomitant bladder cancer, possibly creating a selection bias. Despite these limitations, our study has strengths, such as a centralized pathologic review and standardized follow-up.

Conclusion

Patients with preoperative anemia had a greater probability of having UTUC with higher tumor stages, higher tumor grades, and LNM (pN+). Preoperative anemia was an independent predictor of EUR and CSS in patients who underwent RNU. Identification of preoperative prognostic factors for relapse and survival is essential for easier decision making in relation to management of patients with UTUC, consideration of neoadjuvant therapy, and selection of patients who would benefit from inclusion into clinical trials.

Clinical Practice Points

- Anemia is the most common and most persistent hematologic abnormality faced by cancer patients.
- Because of the rarity of the disease, the significance of preoperative anemia has not been clearly established in UTUC.
- We found that preoperative anemia was an independent predictor of EUR and CSS in patients who underwent RNU.
- Patients with preoperative anemia had a greater probability of having UTUC with higher tumor stages, higher tumor grades, and LNM.
- An improved understanding of the prognostic parameters may lead to the identification of patients who may benefit from intensified therapy and monitoring.

Acknowledgments

This work was supported by the Ministry for Science and Technology of the Republic of Serbia, through contact 175042 (2011-2014).

Disclosure

The authors have stated that they have no conflicts of interest.

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