

Original Article

2-year result of neoadjuvant chemotherapy for upper urinary tract transitional cell carcinoma

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Abstract

Objective: To determine whether neoadjuvant chemotherapy has any benefit in comparison to the initial surgical procedure in patients with a high-risk disease.

Material and Method: Retrospective review of patients who received neoadjuvant chemotherapy followed by surgery from 2014-2017 (study group), compared to a matched cohort who underwent radical nephroureterectomy with bladder cuff excision as the first step of treatment in the same period (control group). The Fisher exact, Wilcoxon rank-sum and Kaplan-Meier methods were used. The log-rank test and Cox proportional hazards model were used to evaluate the association of these two outcomes with patients, treatment, and tumor characteristics in univariate and multivariate models.

Result: Of 35 patients, 15 were in the study group and 20 in the control group. The neoadjuvant systemic therapy group had an improved overall survival (OS) and disease specific survival (DSS) in the early 2-year follow-up protocol (2-year OS and DSS was 80.2% and 90.1% in the study group, versus 57.6% in the control group). In multivariate analyses the study group had a lower risk of mortality (OS hazard ratio 0.42 [p=0.035]; DSS hazard ratio 0.19 [p=0.006]).

Conclusion: Neoadjuvant with systemic therapy improves the survival of high-risk patients with upper urinary tract transitional cell carcinoma in a matched historical cohort of patients treated with initial radical nephroureterectomy with bladder cuff excision.

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Radical nephroureterectomy with bladder cuff excision is the gold standard for high-grade upper urinary transitional cell carcinoma (UUT-TCC), but several results present poor survival for muscle invasive patients,^[1-6] especially in non-organ confined UUT-TCC or lymph node involvement after en-bloc procedures. Neoadjuvant chemotherapy (cisplatin-based) is an accepted treatment in transitional cell carcinoma of the urinary bladder with a better survival rate.^[7,8] Pre en-bloc resection chemotherapy has an advantage beyond adjuvant chemotherapy due to the high incidence of baseline and subsequent decrease in the function of the kidney following radical nephroureterectomy with bladder cuff excision. Adjuvant systemic therapy is limited by the significant loss of renal function after surgery. Chronic kidney disease has been found in nearly half of UUT-TCC patients, which worsens after en-bloc procedures and precludes adjuvant therapy with cisplatin-based therapy, with only less than 22% of patients having normal renal function.^[9,10]

Martin SF and colleagues in 2010 presented the significant rates of disease downstaging and a 14% rate of complete response after neoadjuvant systemic therapy for high-risk UUT-TCC patients who underwent a radical nephroureterectomy with bladder cuff excision compared with the control group who underwent en-bloc surgery without neoadjuvant protocol.^[10] A study by Igawa in 1995 reported that 15 patients with locally advanced UUT-TCC had a 13% complete remission rate and improved survival in this group.^[11] Survival benefits were an objective of the current study in order to determine whether neoadjuvant chemotherapy has any benefit in comparison to the initial surgical procedure in patients with a high-risk disease.

Material and Method

According to the current data, UUT-TCC patient survival had not improved with adjuvant systemic therapy. In 2015 we began offering neoadjuvant

chemotherapy to this group with high-risk features at our hospital. The criteria used to identify high-risk UUT-TCC patients to be considered for neoadjuvant systemic therapy were sessile tumor characteristics^[12], high-grade tumor from biopsy or urine cytology specimens,^[13] and a large tumor burden (measurable on axial imaging).^[14,15] This became our standard regimen based on the retrospective studies available and standard protocol for muscle invasive bladder cancer.

The study group thus comprised UUT-TCC patients who received neoadjuvant chemotherapy followed by radical nephroureterectomy with bladder cuff excision at Phramongkutklo Hospital from 2014-2017. The control group consisted of patients who underwent en-bloc surgery in same period without pre-surgical chemotherapy.

From patient records we evaluated multi clinical and pathologic features, including patient data (age, gender, Eastern Cooperative Oncology Group (ECOG) performance status), tumor data (laterality, radiographic tumor size, prior history of bladder cancer, location of tumor, tumor architecture), treatment (type and courses of neoadjuvant chemotherapy, lymphadenectomy performed), pathology (pathologic classification, pathologic nodal classification, number of lymph nodes removed; and presence of extranodal extension, lymphovascular invasion, carcinoma in situ (CIS), and multifocality), and survival (disease specific survival (DSS) and overall survival (OS)). Pathologic complete remission was defined as the absence of any identifiable malignancy in all resected specimens.

The Fisher exact test and Wilcoxon rank-sum test were used to compare categorical and continuous patient characteristics, respectively. The Kaplan-Meier method was used to estimate the probability of overall survival and disease-specific survival rates starting from surgery. Patients who were lost to follow-up or died due to other reasons were censored. The log-rank test and Cox proportional hazards model were used to evaluate the association of these two time-to-event outcomes with patient characteristics, treatments,

and tumor characteristics.

Clinically relevant variables and variables that were significant in univariate analysis were included in the multivariate model. Age, neoadjuvant chemotherapy and sessile architecture were significant in univariate analysis for both OS and DSS. Number of lymph nodes was added to the model as surrogates to control the differences over time in the surgical management and principles of lymphadenectomy for UUT-TCC. The mere performance of a lymphadenectomy as well as the total number of lymph nodes removed was not significantly associated with DSS or OS in univariate analysis. Roscigno and colleagues reported in a retrospective study that at least 8 lymph nodes are necessary in order to consider lymphadenectomy in UUT-TCC sufficient,^[16] and therefore we used this cut-off in our analysis as a surrogate to account for the differences in surgical technique. Lymphadenectomy in the study group included the paracaval or paraaortic lymph nodes, and interaortocaval lymph nodes in those with tumors above the mid ureter, while pelvic lymphadenectomy was performed for those with distal ureteral tumors. SAS software 9.3 (SAS Institute Inc., Cary, NC) and S plus software 8.2 (TIBCO software Inc., Palo Alto, CA) were used for statistical analyses. P-values <0.05 were considered statistically significant.

Result

The study group consisted of 15 patients who received neoadjuvant systemic therapy. The control group consisted of 20 patients who underwent radical nephroureterectomy with bladder cuff excision without pre-surgical regimen. Table 1 lists the results of baseline, surgery, and tumor characteristics of the two groups based on the Fisher exact tests and Wilcoxon rank-sum tests. Differences in laterality seemed spurious, and the lower incidence of lymphadenectomy in the study group reflects changing trends in the treatment of the disease. Five (25%) of

the patients in the control group received adjuvant chemotherapy while in the study group none received the post-surgical regimen. There was no statistical difference ($p=0.416$) in tumor size (mean, \pm SD) in 10/20 patients who underwent initial surgery (4.1 cm \pm 2.1) compared with 9/15 patients who received neoadjuvant chemotherapy (3.7 \pm 1.3).

Neoadjuvant therapy consisted of a cisplatin-containing protocol in 15 patients (cisplatin-gemcitabine). All patients who were started on neoadjuvant chemotherapy were able to complete 4 cycles prior to radical nephroureterectomy with bladder cuff excision. No patient was precluded from surgery because of neoadjuvant chemotherapy.

Significant differences in disease staging between the study population and the control group were observed in individual stages or various stage subgroupings. There was a significantly lower rate of muscle-invasive ($p=0.0017$) and organ-confined disease ($p=0.0024$) in the study population versus the control group when evaluating only those with pN0 disease (table 2). Downstaging remained significant when including pN+ patients ($p=0.001$ and 0.0005 , respectively). There was no difference in the rates of pN1-2 disease in the control and study groups (18.2% and 6.5%, respectively, $p=0.2218$). The 2-year OS and DSS rate was 80.2% and 90.1% in study group, versus 57.6% in control group.

Multivariate analyses were performed to assess the effects of individual factors on outcomes. Variables that were significant and clinically relevant in univariate analyses were included in multivariate models as described in the Methods section. Cox regression models for overall survival showed neoadjuvant chemotherapy to have a significant influence on overall survival (Table 3). Age, number of lymph nodes removed and tumor architecture were not significant in the model. Similar analyses for disease-specific survival showed significant influence of neoadjuvant chemotherapy and tumor architecture (Table 3).

Table 1. Patient and tumor characteristics in those who received neoadjuvant chemotherapy and patients who did not. (Fisher exact and Wilcoxon rank-sum tests)

Characteristic		Number of patients (%)		p value
		Radical nephroureterectomy with bladder cuff excision (N=20)	Neoadjuvant chemotherapy then radical nephroureterectomy with bladder cuff excision (N=15)	
Age (median, range)		71 (42-86)	68 (45-80)	0.8664
Sex	Female	8 (40)	6 (40)	1
	Male	12 (60)	9 (60)	
ECOG	0	11 (55)	9 (60)	0.3009
	1	9 (45)	6 (40)	
Laterality	Left	12 (60)	10 (66.67)	0.4051
	Right	8 (40)	5 (33.33)	
Location	Pelvis	13 (65)	11 (73.33)	0.356
	Ureter	7 (35)	4 (26.67)	
Previous TCC of urinary bladder	No	9 (45)	7 (46.67)	0.631
	Yes	11 (55)	8 (53.33)	
Lymphadenectomy	No	8 (40)	3 (20)	0.0259
	Yes	12 (60)	12 (80)	
Architecture of tumor	Papillary	8 (40)	5 (33.33)	0.4051
	Sessile	12 (60)	10 (66.67)	
Adjuvant chemotherapy	No	15 (75)	15 (100)	0.0015
	Yes	5 (25)	0 (0)	
Lymphovascular invasion	No	9 (45)	8 (53.33)	0.623
	Yes	11 (55)	7 (46.67)	
Carcinoma in situ	No	8 (40)	8 (53.33)	0.592
	Yes	12 (60)	7 (46.67)	
Mutifocality	No	11 (55)	8 (53.33)	0.142
	Yes	9 (45)	7 (46.67)	

Table 2. Pathologic stage classification inpatients without nodal disease (pN0) who received neoadjuvant chemotherapy and patients who underwent only en-bloc surgery

Pathologic stage classification		Number of patients(%)		p value
		Radical nephroureterectomy with bladder cuff excision (N=20)	Neoadjuvant chemotherapy then radical nephroureterectomy with bladder cuff excision (N=15)	
pT-classification	T0	0	2 (13.33)	0.0011
	Ta	2 (10)	2 (13.33)	
	Tis	2 (10)	1 (6.67)	
	T1	2 (10)	4 (26.67)	
	T2	4 (20)	3 (20)	
	T3	8 (40)	2 (13.33)	
	T4	2 (10)	1 (6.67)	

Table 3. Multivariate Cox model for 2-year overall survival and disease-specific survival.

Variable	HR (95% CI)	p value
Overall survival		
Age	1.02 (0.998-1.05)	0.075
Neoadjuvant chemotherapy	0.42 (0.19-0.94)	0.035
>8 lymph nodes removed	0.75 (0.40-1.40)	0.370
Sessile tumor architecture	1.16 (0.69-1.96)	0.580
Disease-specific survival		
Age	1.01 (0.98-1.04)	0.560
Neoadjuvant chemotherapy	0.19 (0.06-0.61)	0.006
>8 lymph nodes removed	0.54 (0.24-1.23)	0.140
Sessile tumor architecture	2.77 (1.30-5.89)	0.008



Discussion

Systemic chemotherapy used before radical nephroureterectomy with bladder cuff excision is associated with better overall and disease-specific survival as compared to a matched cohort of patients treated with initial surgery.

Igawa and colleagues^[11] showed that the majority of UUT-TCC patients present with chronic kidney disease, and an even greater proportion cannot receive effective post-surgical systemic therapy when adverse pathologic features are found.^[9] This result may explain the conflicting and largely inconclusive reports from old studies on the utility of adjuvant chemotherapy for UUT-TCC cases.^[17-22]

Ureteroscopy is an advanced technology that provides both earlier disease detection and treatment. However, survival rates for UUT-TCC patients have not improved and may even be worsening.^[23] These developments indicate that the treatment paradigm for UUT-TCC may need to be shifted from reflexive initial surgery to more accurate and thoughtful risk stratification with the consideration of neoadjuvant systemic therapy for high-risk cases.

Retrospective analysis is the limitation of this study. Reanalysis of any equivocal pathologic report was conducted and excluded those found that were not high-grade tumors. The survival rates for the control group were similar to the survival rates in other previous UUT-TCC studies, which supports the use of this group as a historical matched control. Margulis and colleagues reported a study of 1,363 patients with UUT-TCC who underwent en-bloc surgery and found that patients with a high-grade disease had a 5-year survival of 57.2%^[4]. The same result from 1998 by Hall and colleagues showed that 252 cases with UUT-TCC who underwent radical nephroureterectomy with bladder cuff excision had a disease-specific survival rate of 40.5-72.6% for patients with T2-4 disease.^[1] Those data support the validity of our control

group. In some studies of neoadjuvant treatment, the pathologic outcomes showed downstaging for each individual UUT-TCC patient, so it is not possible given the inaccuracy of the initial clinical staging. Clinical stage is thought to have a wrong classification bias of approximately 45% and current expert opinion, as well as many retrospective reports, has shown tumor grade as a stronger predictor of high-risk disease with a strong association with advanced pathologic stage, recurrence, and outcome.^[1,4] It is therefore difficult to control true clinical staging, which adds to the limitations of our findings and conclusion. A small number of cases did have a history of TCC in the urinary bladder. Although this was not significantly different between the groups, it may confound findings and outcomes related to disease specific survival. Thus, a randomized trial with matched historical cohorts, such as the one used in this study, could provide better data for assessing patient outcomes.

Conclusion

Neoadjuvant cisplatin-based chemotherapy for high-risk UUT-TCC cases resulted in significantly higher survival rates than did radical nephroureterectomy with bladder cuff excision without pre-operative chemotherapy in a matched historical group.

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