Effect of Body Mass Index and Hypertension on the Prognosis of Upper Tract Urothelial Carcinoma After Radical Nephroureterectomy

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Purpose: To investigate the impact of preoperative underlying hypertension (HTN) and body mass index (BMI) on oncologic outcomes in patients with upper tract urothelial carcinoma (UTUC) who underwent radical nephroureterectomy (RNUx).

Materials and Methods: From May 2003 to December 2018, 453 UTUC patients who underwent RNUx at a single institution were enrolled in the study. All patients were divided into 2 groups according to preoperative HTN and BMI (cutoff 24 kg/m²) and perioperative parameters and recurrence outcomes were compared. Multivariate Cox proportional hazard analysis was performed to identify the significance of HTN and BMI regarding UTUC recurrence.

Results: Among a total 453 UTUC patients, 233 (51.4%) had HTN, and 222 (49.0%) had BMI $\geq$ 24 kg/m². The HTN versus no-HTN group had similar perioperative outcomes, except for the rate of diabetes ($p < 0.001$). The high-BMI versus low-BMI group had similar outcomes, except for the prevalence of HTN ($p = 0.026$). During median follow-up of 23 months, 5-year recurrence-free survival rates were 76.2% in the HTN group and 79.9% in the non-HTN group ($p = 0.002$), and 77.3% in the low-BMI group and 79.0% in the high-BMI group ($p = 0.007$). Multivariate analysis showed that BMI (hazard ratio [HR], 0.740; $p = 0.046$), and HTN (HR, 1.687; $p = 0.005$) were significant predictors of cancer recurrence.

Conclusions: Among UTUC patients who underwent RNUx, patients with HTN and low-BMI showed worse prognosis regarding cancer recurrence. To validate our results, the mechanisms of association between HTN, BMI, and UTUC should be investigated in further prospective studies. (Korean J Urol Oncol 2020;18:201-208)

Key Words: Upper tract urothelial carcinoma · Body mass index · Hypertension · Survival

INTRODUCTION

In a recent survey, the prevalence of urinary tract urothelial carcinoma (UTUC) was 1–2 per 100,000 in the United States, and 4.8 per 100,000 in the Republic of Korea.^{1,2} UTUC is a highly aggressive malignancy, and radical nephroureterectomy (RNUx) is the current standard treatment for patients with the disease.³ The 5-year recurrence-free survival (RFS) estimate was 70% in patients with UTUC treated with radical RNUx.⁴

Received July 24, 2020, Revised September 20, 2020,
Accepted September 25, 2020

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Tumor stage, lymph node metastasis, chronic urinary tract infection, hydronephrosis, and smoking are closely related to recurrence of UTUC.⁵⁻⁹ Hypertension (HTN) and obesity, which are metabolic factors, have been studied regarding cancer. Many studies have reported regarding a relationship between HTN and body mass index (BMI) and renal cell carcinoma, bladder cancer, prostate cancer, breast cancer, and lung cancer.¹⁰⁻¹⁷ However, there are few studies about the relationship between HTN, BMI, and UTUC in patients with RNUx. One study reported that patients with low-BMI ($<18.5 \text{ kg/m}^2$) had a worse prognosis, regarding RFS and cancer-specific survival (CSS), than patients with normal BMI ($18.5\text{--}25 \text{ kg/m}^2$) or obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$).¹⁸ Another study reported that diabetes mellitus was related to post-operative bladder cancer recurrence in China.¹⁹ Therefore, we investigated the influence of HTN and BMI on oncologic outcomes in patients with UTUC treated with RNUx.

MATERIALS AND METHODS

1. Study Population

From May 2003 to December 2018, after obtaining institutional review board approval (B-1907-552-110), UTUC patients who underwent RNUx at one institution were enrolled in the study. We excluded patients with metastasis at the time of RNUx, and patients with incomplete data. Thus, 453 UTUC patients were enrolled.

2. Data Collection and Pathologic Evaluation

Baseline data before RNUx were collected, including pre-operative glomerular filtration rate, tumor location and laterality, and the presence of hydronephrosis, HTN, or concurrent bladder tumor at RNUx. The patient who has HTN defined to who were taking HTN medication regardless of the type of medication before surgery. All surgical specimens after RNUx were processed according to standard pathologic procedures. Tumors were staged according to the 2009 American Joint Committee on Cancer and International Union for Cancer Control tumor-node-metastasis cancer staging system.²⁰ All patients had pathologically confirmed transitional cell carcinoma in the upper urinary tract after RNUx.

RNUx was performed using an open, laparoscopic, or ro-

botic method. Open RNUx was carried out in 164 patients (36.2%), laparoscopic RNUx in 143 (31.6%), and robotic-assisted RNUx in 146 (32.2%). Most open surgery was done by flank incision for nephrectomy, followed by a Gibson incision for distal ureteral resection. Lymph node dissection was performed when enlarged lymph nodes were found on preoperative computed tomography (CT) scans or were palpable during surgery. No patients had known metastatic disease at the time of surgery, as shown by radiography and CT scan.

Patients were generally followed-up every 3 months during the first 2 years after surgery, every 6 months from 2–5 years after surgery, and annually thereafter. Follow-up examinations consisted of history taking, physical examination, routine blood evaluation, urinary cytology, cystoscopic evaluation of the bladder, and radiographic evaluation of the chest and abdomen.

3. Statistical Analyses

Statistical analyses were carried out using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Differences in continuous variables were analyzed by paired t-test. The chi-square test was carried out to assess differences in covariate distribution among the 2 categories. The primary endpoints were RFS, which was defined as the interval between surgery and the subsequent appearance of either local failure (in regional lymph nodes) at the operative site or in the bladder, and distant metastasis. Survival analysis was carried out using the Kaplan-Meier method. Multivariate survival analyses were carried out using the Cox regression model.

RESULTS

Among a total of 453 patients, 233 (51.4%) had a history of HTN (Table 1). There were no significant differences between the HTN and no-HTN groups, except for the rate of diabetes mellitus (27.5% vs. 10.0%, $p<0.001$).

Median BMI was 24.06 kg/m^2 (interquartile range, $21.78\text{--}26.08 \text{ kg/m}^2$) in the 453 patients, among whom 222 (49.0%) had high-BMI ($\geq 24 \text{ kg/m}^2$). High-BMI patients had a higher rate of HTN than the low-BMI group (56.8% vs. 46.3%, $p=0.026$) and a lower rate of transfusions (14.0% vs. 24.7%, $p=0.046$). Other perioperative parameters, including surgical

Table 1. Baseline and perioperative results among 453 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma

Variable	HTN (-) (N=220)	HTN (+) (N=233)	p-value	BMI<24 kg/m ² (N=231)	BMI≥24 kg/m ² (N=222)	p-value
Age (yr)	65.28 (59-73)	70.42 (64-77)	0.152	68.79 (63-77)	67.03 (61-74)	0.345
Sex			0.174			0.138
Male	162 (73.6)	158 (67.8)		156 (67.5)	164 (73.9)	
Female	58 (26.4)	75 (32.2)		75 (32.5)	58 (26.1)	
Smoking			0.240			0.757
Yes	38 (17.3)	31 (13.3)		34 (14.7)	35 (15.8)	
No	182 (82.7)	202 (86.7)		197 (85.3)	187 (84.2)	
ECOG			0.479			0.552
0	8 (3.6)	14 (6.0)		9 (3.9)	13 (5.9)	
1	208 (94.5)	214 (91.8)		217 (93.9)	205 (92.3)	
3-5	4 (1.8)	5 (2.2)		5 (2.2)	4 (1.8)	
Preoperative GFR	73.7 (59.1-86.8)	63.1 (49.4-74.0)	0.495	68.1 (51-82)	68.3 (54-80)	0.776
Laterality			0.054			0.261
Left	109 (49.5)	138 (58.4)		129 (55.8)	116 (52.3)	
Right	111 (50.5)	95 (40.8)		100 (43.3)	106 (47.7)	
Bilateral	0 (0)	2 (0.9)		2 (0.9)	0 (0)	
Location			0.764			0.268
Lower ureter	44 (22.0)	44 (18.9)		41 (17.7)	47 (21.2)	
Mid ureter	18 (8.2)	34 (14.6)		21 (9.1)	31 (14.0)	
Upper ureter	26 (11.8)	35 (15.0)		33 (14.3)	28 (12.6)	
Pelvis	94 (42.7)	67 (28.8)		83 (35.9)	78 (35.1)	
Multiple	38 (17.3)	53 (22.7)		53 (22.9)	38 (17.1)	
Hydronephrosis			0.054			0.546
Yes	138 (62.7)	166 (71.2)		152 (65.8)	152 (68.5)	
No	82 (37.3)	67 (28.8)		79 (34.2)	70 (31.5)	
Diabetes mellitus			<0.001			0.161
Yes	22 (10.0)	64 (27.5)		38 (16.5)	48 (21.6)	
No	198 (90.0)	169 (72.5)		193 (83.5)	174 (78.4)	
HTN						0.026
Yes				107 (46.3)	126 (56.8)	
No				124 (53.7)	96 (43.2)	
Operation method			0.707			0.288
Open	78 (35.5)	86 (36.9)		91 (39.4)	73 (32.9)	
Laparoscopic	67 (30.5)	76 (32.6)		72 (31.2)	71 (32.0)	
Robotic	75 (34.1)	71 (30.5)		68 (29.4)	78 (35.1)	
Mean operation time	225 (185-270)	226.45 (175-267.5)	0.651	224.1 (175-265)	232.0 (180-275)	0.520
Estimated blood loss	267 (100-300)	261.93 (100-300)	0.249	277.0 (100-300)	251.7 (100-300)	0.067
Transfusion rate (%)	20.5	18.5	0.591	24.7	14.0	0.046
Complications	7 (3.2)	9 (3.9)	0.695	7 (3.0)	9 (4.1)	0.555

Values are presented as median (interquartile range) or number (%) unless otherwise indicated.

HTN: hypertension, BMI: body mass index, ECOG: Eastern Cooperative Oncology group, GFR: glomerular filtration rate.

methods, operation time, were similar between the 2 groups.

Clinical and pathologic profiles for the 453 patients were stratified by HTN, and BMI (Table 1). In HTN versus no-HTN patients, significant differences were evident in tumor location ($p=0.012$), tumor laterality ($p=0.054$), and the presence of preoperative diabetes mellitus ($p<0.001$), and

hydronephrosis ($p=0.054$). In low-BMI versus high-BMI patients, a significant difference was evident in the presence of preoperative HTN ($p=0.026$).

Table 2 shows pathologic outcomes according to each group. Overall, 168 patients had pathologic pT3-4 (37.1%). Pathologic stage, grade, and lymph node invasion were sim-

Table 2. Pathologic and survival outcomes in patient who underwent radical nephroureterectomy for upper tract urothelial carcinoma

Variable	HTN (-) (N=220)	HTN (+) (N=233)	p-value	BMI<24 kg/m ² (N=231)	BMI≥24 kg/m ² (N=222)	p-value
T stage			0.162			0.053
Ta	4 (1.8)	2 (0.9)		3 (1.3)	3 (1.4)	
T1	64 (29.1)	63 (27.0)		55 (23.8)	72 (32.4)	
T2	72 (32.7)	75 (32.2)		70 (30.3)	77 (34.7)	
T3	63 (28.6)	82 (35.2)		88 (38.1)	57 (25.7)	
T4	12 (5.5)	11 (4.7)		11 (4.8)	12 (5.4)	
Tis	5 (2.3)	0 (0)		4 (1.7)	1 (0.5)	
Lymph node invasion			0.466			0.525
Nx	125 (56.8)	138 (59.2)		137 (59.3)	126 (56.8)	
N0	41 (18.7)	55 (23.6)		47 (20.3)	49 (22.1)	
≥N1	21 (9.5)	24 (10.3)		21 (9.1)	24 (10.8)	
Grade			0.059			0.553
I	2 (0.9)	0 (0)		0 (0)	2 (0.9)	
II	113 (51.4)	112 (48.1)		115 (50.2)	110 (49.5)	
III	101 (45.9)	121 (51.9)		114 (49.8)	108 (48.6)	
Positive surgical margin (%)	15 (6.8)	15 (6.4)	0.871	21 (9.1)	9 (4.1)	0.031
Recurrence (%)	122 (55.5)	152 (65.2)	0.033	149 (64.5)	125 (56.3)	0.074
Recurrence site						
Bladder	69	84		79	74	
Lymph node	52	67		64	55	
Lung	33	35		37	31	
Bone	16	28		27	17	
Liver	16	18		18	16	
Local	8	15		11	12	
Others*	34	48		46	36	
Cancer specific survival (%)	207 (94.1)	214 (91.8)	0.802	212 (91.8)	209 (94.1)	0.300
Overall survival (%)	199 (90.5)	208 (89.3)	0.661	200 (86.6)	207 (93.2)	0.143
Adjuvant chemotherapy (%)	66 (30.0)	69 (29.6)	0.880	67 (29.0)	68 (30.6)	0.683

Values are presented number (%).

HTN: hypertension, BMI: body mass index.

*Others: prostate, pelvic cavity, colorectal, adrenal, brain, etc.

ilar between the groups. The positive surgical margin was greater in the low-BMI than high-BMI group (9.1% vs. 4.1%, $p=0.031$). During 42.0-month follow-up, cancer recurrence was observed in 274 patients (60.5%). The most frequent sites of recurrence were the bladder (153 of 453 patients, 33.8%), lymph nodes (119 of 453, 26.3%), lung (68 of 453, 15.0%), and bone (44 of 453, 9.7%). Adjuvant chemotherapy rate was no significantly difference between HTN and no-HTN patients (29.6% vs. 30.0%, $p=0.880$), also no significantly difference between low-BMI and high-BMI group (29.0% vs. 30.6%, $p=0.683$). Cancer recurrence was more frequent in the HTN than no-HTN group (65.2% vs. 55.5%, $p=0.033$). Five-year RFS rates were 76.2% in the HTN group and 79.9% in the no-HTN group (log-rank,

$p=0.002$) (Fig. 1), and those were 77.3% in the low-BMI group and 79.0% in the high-BMI group (log-rank, $p=0.007$) (Fig. 2). Five-year intravesical RFS rates were no significant difference in the HTN group and in the no-HTN group (66.4% vs. 65.7%, log-rank $p=0.120$), also no difference in low-BMI group and in the high-BMI group (67.4% vs. 64.7% log-rank $p=0.438$).

Multivariate Cox proportional hazard analysis showed the significance of BMI and HTN in relation to cancer recurrence after adjusting for other factors (Table 3). That is, BMI (hazard ratio [HR], 0.740; 95% confidence interval [CI], 0.551-0.995; $p=0.046$) and HTN (HR, 1.687; 95% CI, 1.174-2.426; $p=0.005$) were significant predictors of cancer recurrence. That is, BMI (hazard ratio [HR], 0.740; 95%

Fig. 1. Kaplan-Meier analysis of the association of hypertension (HTN) with recurrence-free survival in 453 patients with upper tract urothelial carcinoma treated with radical nephroureterectomy.

confidence interval [CI], 0.551-0.995; $p=0.046$) and HTN (HR, 1.687; 95% CI, 1.174-2.426; $p=0.005$) were significant predictors of cancer recurrence.

Five-year OS rates were no significant difference in the HTN group and in the no-HTN group (89.3% vs, 90.5%, log-rank $p=0.661$), also no difference in low-BMI group and in the high-BMI group (86.6% vs, 93.2% log-rank $p=0.143$). Five-year CSS rates were no significant difference in the HTN group and in the no-HTN group (91.8% vs. 94.1%, log-rank $p=0.802$), also no difference in low-BMI group and in the high-BMI group (91.8% vs. 94.1% log-rank $p=0.300$) (Table 2). Multivariate Cox proportional hazard analysis showed that BMI and HTN are not significantly related to OS and CSS after adjusting for other factors (Tables 4, 5).

DISCUSSION

Although UTUC is not a common cancer, it has a high recurrence rate. In particular, smoking status, tumor stage, and lymph node metastases are associated with UTUC recurrence. This study assessed how obesity and HTN, which continue to increase in incidence, might be linked to UTUC. Thus, in 453 RNUx-operated UTUC patients, we found that RFS in patients with high-BMI, without HTN, was good. Several papers exist about the relationship between renal cell carcinoma and HTN and BMI, but few

Fig. 2. Kaplan-Meier analysis of the association of body mass index (BMI) with recurrence-free survival in 453 patients with upper tract urothelial carcinoma treated radical nephroureterectomy.

studies have been published about the relationship between UTUC and HTN and BMI.

In one study, when 236 UTUC patients underwent RNUx in China, higher BMI was associated with better RFS and CSS.¹⁸ In another paper, low-BMI was an independent predictor of worse CSS on multivariate analysis in 103 obese patients (HR, 2.210; $p=0.047$).²¹ In patients with high-BMI, increased fat between the kidney and Gerota's fascia may suggest that the higher the BMI, the better will be survival, as UTUC has difficulty in transitioning and invading beyond the fascia.¹⁸ Furthermore, Obesity is associated with hyperinsulinemia, which may increase the secretion of peptide hormones such as leptin and adiponectin. These peptide hormones promote the proliferation and activation of natural killer cells, resulting in antitumor effects.²²

Recently, a large-scale prospective study of 226,505 patients with UTUC reported that HTN was related to UTUC by using univariate analysis. HTN are components of metabolic syndrome, which is involved in cancer development. HTN affects apoptosis, which regulates cell turnover in other solid cancers. HTN also has a metabolic pathway associated with oxidative stress, another cancer-causing factor.²³

In this study, the patient with HTN and low-BMI showed higher recurrence rate than the patient with high-BMI and without HTN (67.6% vs. 47.4% $p=0.013$). Although, BMI and HTN is generally positively correlated, those factors

Table 3. Univariate and multivariate Cox proportional hazard analysis predict significant factors to cancer progression after radical nephroureterectomy in upper tract urothelial carcinoma patients

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.011	0.999–1.023	0.076	-	-	-
BMI (<24 vs. ≥24 kg/m ²)	0.724	0.569–0.921	0.007	0.754	0.589–0.964	0.024
History of smoking	0.956	0.685–1.333	0.789	-	-	-
Adjuvant Chemotherapy	3.389	2.658–4.321	<0.005	2.986	2.250–3.962	<0.005
Tumor stage (≥T3 or not)	2.142	1.683–2.726	<0.005	1.085	0.814–1.446	0.579
Tumor grade (≥3 or not)	1.156	0.909–1.469	0.236	-	-	-
Lymph node invasion	1.377	1.083–1.751	0.009	1.236	0.964–1.585	0.095
Positive surgical margin	2.789	1.890–4.114	<0.005	2.355	1.580–3.510	<0.005
Postoperative GFR	0.997	0.991–1.003	0.411	-	-	-
Presence of preoperative Hydronephrosis	1.444	1.101–1.892	0.008	1.174	0.889–1.551	0.258
Presence of preoperative DM	1.130	0.836–1.527	0.431	-	-	-
Presence of preoperative HTN	1.446	1.135–1.842	0.002	1.492	1.167–1.908	0.001

HR: hazard ratio, CI: confidence interval, BMI: body mass index, GFR: glomerular filtration rate, DM: diabetes mellitus, HTN: hypertension.

Table 4. Univariate and multivariate Cox proportional hazard analysis predict significant factors to overall survival on after radical nephroureterectomy in upper tract urothelial carcinoma patients

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.085	1.046–1.126	<0.005	1.108	1.061–1.156	<0.005
BMI (<24 vs. ≥24 kg/m ²)	0.467	0.251–0.868	0.016	0.102	0.314–1.111	0.102
History of smoking	0.651	0.257–1.652	0.367	-	-	-
Adjuvant Chemotherapy	3.737	2.056–6.792	<0.005	3.916	1.868–8.210	<0.005
Tumor stage (≥T3 or not)	4.770	2.531–8.991	<0.005	2.148	1.025–4.498	0.043
Tumor grade (≥3 or not)	1.230	0.680–2.226	0.494	-	-	-
Lymph node invasion	1.214	0.676–2.181	0.515	-	-	-
Positive surgical margin	2.730	1.067–6.892	0.036	1.266	0.493–3.250	0.623
Postoperative GFR	1.008	0.993–1.023	0.286	-	-	-
Presence of preoperative Hydronephrosis	1.043	0.554–1.960	0.897	-	-	-
Presence of preoperative DM	1.664	0.656–4.223	0.283	-	-	-
Presence of preoperative HTN	1.309	0.728–2.354	0.368	-	-	-

HR: hazard ratio, CI: confidence interval, BMI: body mass index, GFR: glomerular filtration rate, DM: diabetes mellitus, HTN: hypertension.

can affect in a contradictory manner. A study showed that obese patients had lower mortality by cardiovascular and ischemic heart disease than non-obese patients in hypertensive patients.²⁴ Like this research, BMI and HTN can act as independent variables and even obesity showed protective effects in some studies regarding UTUC patients. But it is difficult to clearly describe underlying pathophysiology of this contradictorily looking phenomenon. This is considered to be a limitation, and further investigation would be needed.

Our study has several limitations. First, as a retrospective study, each patient had a different follow-up period, and various biases were generated, such as inability to adjust the treatment method for UTUC. Second, BMI and HTN were assessed just before surgery, but all patients who underwent surgery were not being treated for HTN, so it was unclear how well HTN was being treated and controlled. Third, the effect of HTN and BMI on OS and CSS in UTUC patients was investigated, but there was no statistically significant difference in this study. Despite these limitations, our paper

Table 5. Univariate and multivariate Cox proportional hazard analysis predict significant factors to cancer specific survival on after radical nephroureterectomy in upper tract urothelial carcinoma patients

Variable	Univariate analysis			Multi-variate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.059	1.012–1.108	0.013	1.092	1.032–1.155	0.002
BMI (<24 vs. ≥24 kg/m ²)	0.797	0.368–1.724	0.564	-	-	-
History of smoking	0.664	0.199–2.211	0.504	-	-	-
Adjuvant Chemotherapy	10.480	3.948–27.819	<0.005	8.632	2.840–26.237	<0.005
Tumor stage (≥T3 or not)	8.934	3.360–23.751	<0.005	2.850	0.978–8.302	0.055
Tumor grade (≥3 or not)	1.066	0.493–2.308	0.870	-	-	-
Lymph node invasion	1.282	0.594–2.766	0.527	-	-	-
Positive surgical margin	5.013	1.869–13.445	0.001	2.306	0.864–6.153	0.095
Postoperative GFR	1.006	0.987–1.026	0.548	-	-	-
Presence of preoperative Hydronephrosis	1.324	0.600–2.919	0.487	-	-	-
Presence of preoperative DM	1.637	0.491–5.454	0.422	-	-	-
Presence of preoperative HTN	1.844	0.835–4.069	0.130	-	-	-

HR: hazard ratio, CI: confidence interval, BMI: body mass index, GFR: glomerular filtration rate, DM: diabetes mellitus, HTN: hypertension.

suggests that HTN and BMI tend to relapse in UTUC. Therefore, further prospective studies are needed to investigate the relationship between HTN, BMI, and UTUC.

CONCLUSIONS

Among UTUC patients who underwent RNUx, HTN versus no-HTN was associated with worse RFS. Further, low-BMI (<24 kg/m²) was associated with worse RFS than high-BMI. Future prospective studies are required to validate our results, and basic or translational research should be conducted to determine potential mechanisms for the relationships between HTN, BMI, and UTUC.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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