Bimodal Pattern of the Impact of Body Mass Index on Cancer-specific Survival of Upper Urinary Tract Urothelial Carcinoma Patients

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Abstract. *Aim: To clarify how body mass index (BMI) affects the risk of death from upper urinary tract urothelial carcinoma (UUTUC) we investigated the impact of BMI on UUTUC using a Japanese multicenter database. Patients and Methods: Between January 1995 and December 2010, 1,329 patients with upper urinary tract tumors were treated in 13 institutions in Japan. From this group, a cohort of 1,014 patients treated with radical nephroureterectomy was retrospectively reviewed. BMI was categorized into the following three groups: BMI <22.5, BMI 22.5 to <25 and BMI ≥25. The association between each group and cancer-specific survival (CSS) was analyzed using Cox proportional hazards regression models. Results: The median BMI was 22.4 kg/m^2 (interquartile range, 20.5-24.8). Out of all patients, 213 (21%) died of UUTUC. Hazard ratios of the BMI ≥25 and the BMI <22.5 group were 1.76 and 1.66, respectively. Conclusion: Both higher and lower BMI affect the prognosis of UUTUC treated with radical nephroureterectomy.*

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Key Words: Upper tract urothelial carcinoma, body mass index, obesity, sex difference.

The global incidence of obesity is on the rise and more than one billion adults are now classified as overweight, including 300 million obese people (1). There are many large-scale epidemiological studies that have evaluated the associations between body mass index (the weight in kilograms divided by the square of the height in meters; BMI) and a wide range of disease outcomes (2-4). In upper urinary tract urothelial carcinoma (UUTUC) the association between BMI and the risk of death has been investigated in Western and Asian cohorts but the results of these studies oppose one another. It has been reported that higher BMI is associated with a worse prognosis in a Western cohort and a lower BMI is associated with a worse prognosis in an Asian cohort (5, 6). We hypothesized that these results do not actually conflict with each other and, to clarify how BMI affects the risk of death from UUTUC, we investigated the impact of BMI on UUTUC using a Japanese multicenter database.

Patients and Methods

Patients and patient classification. Between January 1995 and December 2010, 1,329 patients with upper urinary tract tumors were treated in 13 institutions in Japan. The clinicopathological information of these patients was stored in a database (Tokyo Metropolitan Database of Urologic disease) (7). Ethical board review approval was obtained for each hospital. After excluding 265 patients who had not been treated with nephroureterectomy , 40 patients who had been treated with concurrent radical cystectomy and 10 whose data has missing values, 1,014 patients were analyzed. The primary outcome measure was cancer-specific survival (CSS).To investigate the impact of BMI on the CSS of UUTUC, laterality, age, sex, Eastern cooperative oncology group (ECOG) performance status, smoking status (never or current/ex-smoker), body mass index (BMI), pathologic T (pT) stage (pTis/a/1, pT2, pT3, pT4), pathological tumor grade, lymph node status (pN0, pNx, pN1-2) and lymph vascular invasion (LVI) were adjusted for. Clinical parameters were inspected from patients' medical records. Surgical specimens were examined by a genitourinary pathologist in each hospital. Pathologic T stage and lymph node status were assigned according to the 2002 Union for International Cancer Control TNM classification (8). Tumors were graded in accordance with the 1973 WHO/International Society of Urological pathology consensus classification (9).

BMI standards for inclusion to the study and statistical analyses. BMI was categorized into the following three groups: BMI 22.5 to < 25, BMI ≥25 and BMI <22.5 in accordance with the Asia Cohort Consortium BMI project (10). The association between higher and lower BMI and CSS was analyzed using Cox proportional hazards regression models adjusted for other clinical and pathological factors. Using the BMI 22.5 to <25 group as the reference, we estimated the hazard ratios and 95% confidence intervals (CI) for the BMI ≥25 group and the BMI <22.5 group after adjusting for the established parameters (11).

Statistical tests were two-sided, and a *p*-value <0.05 was taken as a measure of statistical significance. All statistical calculations and analyses were performed with R 2.15.0 (The R Foundation for Statistical Computing 2011, link or supplier).

Table I. *Patients' characteristics*.

Variables	Total No. %	Female No. (%)	Male No. (%)	*p*-Value
Gender				
Male	718 (29)			
Female	296 (71)			
Age, years				
Median (IQR)	70 (62-76)	71 (65-78)	69 (61-75)	<0.001
ECOG PS				
0	900 (89)	249 (84)	651 (91)	
≥1	114 (11)	47 (16)	67 (9)	0.349
Smoking status				
Current, ex-smoker	561 (55)	62 (21)	499 (69)	
Non-smoker	453 (45)	234 (79)	219 (31)	0.354
BMI				
Median (IQR)	22.5 (20-25)	22 (20-25)	23 (21-25)	0.704
BMI (categorized)				
BMI<22.5	512 (50)	154 (52)	358 (50)	
BMI 22.5 to <25	221 (22)	84 (28)	197 (27)	
BMI≥25	281 (28)	58 (20)	163 (23)	0.643
Laterality				
Right	477 (47)	151 (51)	326 (46)	
Left	537 (53)	145 (49)	392 (54)	0.041
Dominant tumor grade				
Grade 3	287 (29)	96 (32)	191 (27)	
Grade 1 or 2	702 (71)	200 (68)	527 (73)	<0.001
Pathological T stage				
pTis/a/1	303 (30))	78 (6)	225 (31)	
pT2	147 (15)	48 (16)	99 (14)	
pT3	499 (49)	151 (51)	348 (49)	
pT4	31 (3)	10 (3)	21 (3)	0.348
LVI				
Present	408 (40)	131 (44)	277 (39)	0.021
Lymph node metastasis				
Present	104 (10)	37 (13)	67 (9)	0.390

ECOG PS, Eastern Cooperative Oncology Group Performance status; BMI, body mass index.

Results

The demographics of the patients are listed in Table I. Out of all patients in our cohort, 213 (21%) died of UUTUC. The median follow-up period was 38 months (interquartile range, 16-73), and 5- and 10-year survival rates were 74 and 69%, respectively (Figure 1). The median BMI was 22.4 kg/m^2 (interquartile range, 20.5-24.8). The BMI of the male and female subsets showed almost the same distribution (Figure 2). Distributions of patients for age (p<0.001) and ECOG performance status (p=0.015) were significantly different in each of the BMI groups. After adjusting for the factors, without including BMI, multivariate analysis revealed that factors which affected CSS included pathologic T stage (pT2, pT3 and pT4), pathologic grade (grade 3), lymph node status (pN1-2), LVI (present) and BMI (BMI ≥25 and BMI ≤22.5). Hazard ratios of the BMI ≥25 group and the BMI <22.5 group were 1.76 and 1.66, respectively (Table II). The five-year CSS rates for both these groups were significantly worse than that for the BMI 22.5 to <25 group (Figure 3). When the male and female subsets were analyzed separately (Table III), pathologic T stage (pT3, pT4), pathologic grade (grade 3), lymph node status (pN1-2) and LVI (present) were still significant predictors, while the lower BMI among male patients and the higher BMI among female patients was significantly associated with their poor CSS (Figures 4 and 5). ECOG performance status and lower BMI were significant predictors only in the male subset. In contrast, higher BMI and age were significant factors only in the female subset of patients.

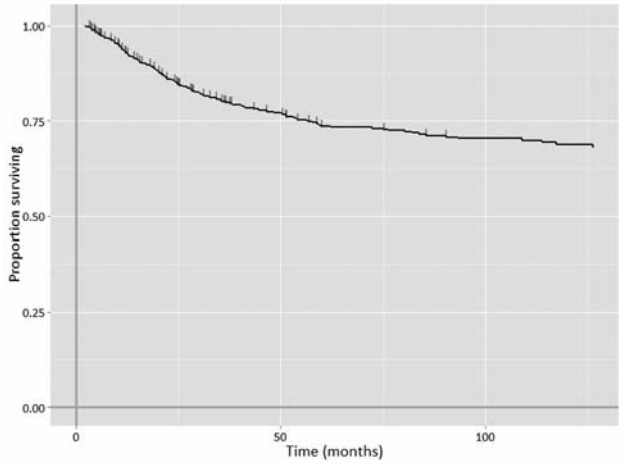

Figure 1. *Kaplan–Meier estimates of disease-specific survival in the entire cohort.*

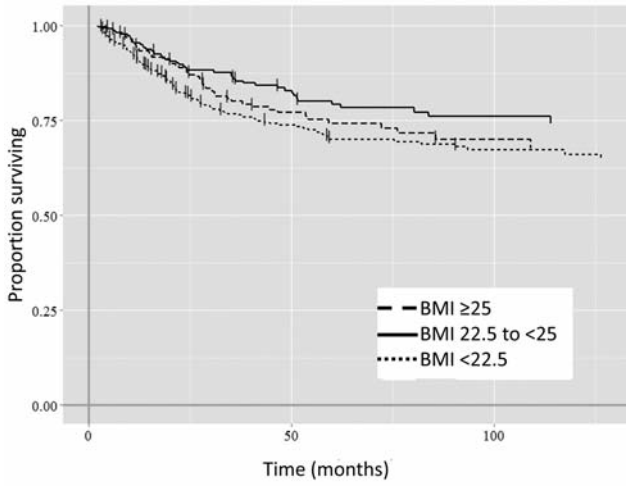

Figure 3. *Kaplan–Meier estimates of disease-specific survival according to BMI group.*

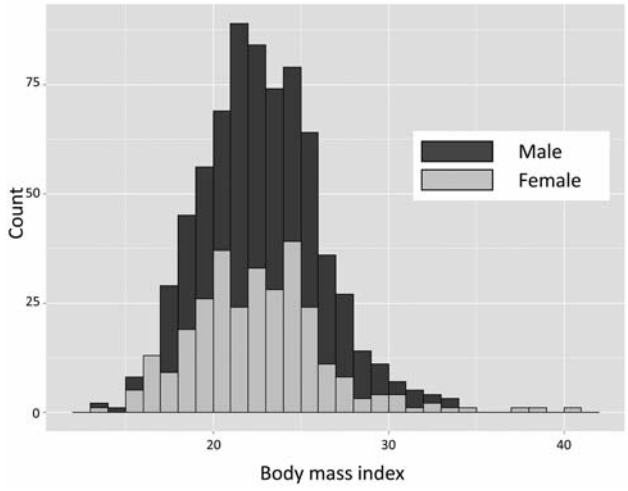

Figure 2. *Distribution of body mass index (BMI) according to gender.*

Discussion

In the present study, both a low and a high BMI were associated with an increased risk of death from UUTUC. A few studies which investigated the association between BMI and the risk of death from UUTUC have been reported, and a worse prognostic outcome was associated with a higher BMI in a Western cohort and a lower BMI in an Asian cohort (5, 6). The reason for such a discrepancy is unknown. No study has yet clarified whether BMI has a positive or negative correlation with CSS. In our study, we demonstrated the bimodal effect of BMI, which is not in conflict with either study.

This is the first study which demonstrates the V-shaped association between BMI and the risk of death from UUTUC. In all-cause mortalities (4, 12), and several specific diseases such as cardiovascular disease (13) and colorectal cancer (14, 15), it has been reported that the association between BMI and risk of each cause is represented by the bimodal hazard ratio's so-called U-shaped figure. In those studies, the positive association between lower BMI and risk of death is more remarkable in Asian populations. In our cohort, the distribution of BMI is more skewed towards the lower end and it is one reason why a lower BMI and CSS of UUTUC had a positive association, while a higher BMI and CSS had a positive association in the report from a Western country. From this different viewpoint, it could be seen that the cohort in this study and that in the Western country are in accordance with and complement each other.

As a result, we found that the relative risk of CSS in higher and lower BMI showed an inverse pattern, which can be explained by the fact that the male patients with a lower BMI and the female patients with a higher BMI had a positive association with CSS. We have demonstrated different prognostic impacts on CSS from gender-segregated subsets. We might be able to attribute the inverse effect on CSS between males and females to the hormonal environment of the patients. In particular, it has been reported that estrogen had at least some association with the prognosis of urothelial carcinoma, and one of the effects might be explained by the fact that the estrogen receptor-β is responsible for a malignant transformation of urothelial carcinoma (16, 17) and an increased aromatization in obese post-menopausal women (18). Among women, it is reported that an increasing BMI was associated with an increased incidence of many cancers,

Table II. *Multivariate Cox proportional hazard regression analysis in the entire cohort.*

	Univariate			Multivariate		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Laterality (right)	0.76	0.52-1.10	0.145			
Gender (male)	1.22	0.77-1.94	0.408			
Age (years)	1.03	1.01-1.06	0.004	1.02	1.01-1.04	0.008
BMI (categorized)						
BMI <22.5	1.38	0.88-2.18	0.165	1.621	1.11-2.38	0.014
BMI 22.5 to <25	ref	-	-	ref	-	-
BM I≥25	1.55	0.91-2.64	0.105	1.68	1.076-2.61	0.022
ECOG PS≥1	1.40	0.80-2.45	0.236			
Smoking status						
Current/ex-smoker	0.91	0.59-1.39	0.655			
Tumor grade 3	2.22	1.51-3.28	<0.001	1.73	1.26-2.38	0.001
Pathologic T stage						
pTis/a/1	ref	-	-	ref	-	-
pT2	2.46	0.96-6.29	0.060	2.846	1.28-6.35	0.011
pT3	4.16	1.86-9.30	<0.001	4.906	2.41-9.98	<0.001
pT4	5.54	1.90-16.13	0.003	8.988	3.76-21.48	<0.001
LVI	2.79	1.74-4.47	<0.001	2.396	1.62-3.56	<0.001
Lymph node metastasis						
	2.81	1.85-4.27	<0.001	2.81	1.98-3.99	<0.001

ECOG PS, Eastern Cooperative Oncology Group Performance status; BMI, body mass index.

Table III. *Multivariate Cox proportional hazard regression analysis according to gender.*

	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (years)	1.02	0.99-1.04	0.077	1.03	0.99-1.06	0.058
BMI (categorized)						
BMI <22.5	1.65	1.03-2.66	0.039	1.16	0.59-2.29	0.672
BMI 22.5 to <25	ref	-	-	ref	-	-
BM I≥25	1.15	0.64-2.06	0.646	2.28	1.10-4.74	0.028
Tumor grade 3	2.03	1.34-3.07	0.001	1.35	0.78-2.31	0.277
Pathologic T stage						
pTis/a/1	ref	-	-	ref	-	-
pT2	2.61	1.01-6.70	0.047	4.40	0.91-21.39	0.066
pT3	4.52	1.99-10.23	<0.001	6.66	1.54-28.86	0.011
pT4	15.49	5.52-43.45	<0.001	6.63	1.15-38.45	0.035
LVI	1.97	1.22-3.17	0.005	3.17	1.49-6.74	0.003
Lymph node metastasis	2.94	1.91-4.53	<0.001	2.48	1.30-4.71	0.006

BMI, Body mass index.

including those hormonally-related and of non-related neoplasm, especially in post-menopausal women (19).

The high risk of UUTUC mortality with decreasing BMI among men is difficult to interpret. In contrast to various speculations about the association between higher BMI and the risk of death from various diseases, there is limited evidence that could account for the association between lower BMI and risk of death from malignant diseases (20, 21). The first reason is that the patients with aggressive and high-stage diseases are often lean and there might be a reverse causation between lower BMI and risk of death from UUTUC. The second reason is that this result could be explained by the smoking status. The rates of current/ex-smoker and non-smoker status in male and female cohorts are quite different. Various population-based studies have indicated that the male gender is confounded by smoking status. Although our study did not indicate that smoking was a potential confounding factor after statistical adjustment, CSS still might be affected by the smoking status of the subjects.

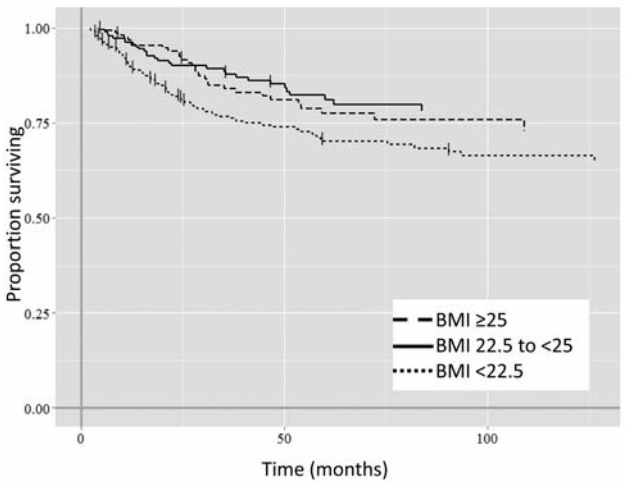

Figure 4. *Kaplan–Meier estimates of disease-specific survival according to BMI group in the male subset.*

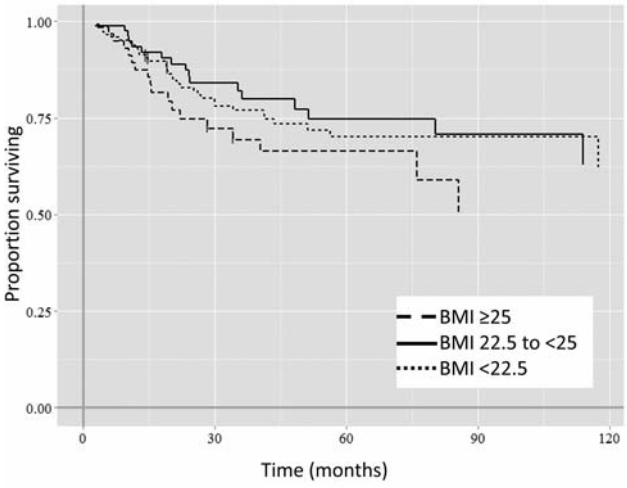

Figure 5. *Kaplan–Meier estimates of disease-specific survival according to BMI group in the female subset.*

Based on our findings, we could conclude that sex difference is an important factor in regard to the association between BMI and CSS of UUTUC. Although it is difficult to interpret the association between BMI and the risk of death from various diseases, because BMI is affected by many confounding factors relating to the etiology of diseases, by taking our results into consideration, research into sex-related hormones and the biology of urothelial cancers could be advanced.

Our study has several limitations and results have to be interpreted with caution. First, although we have attempted to adjust for confounding factors, including disease aggressiveness and smoking status by multivariate statistical analysis and also those which proved to be non-confounding factors, the extremely high smoking rates in male UUTUC patients in our cohort is still a concern. The relation between smoking status and prognosis of UUTUC should be investigated in the future. Second, similar to the median BMI from the previous report on an Asian population, the median BMI in this study was 22.4, which is much lower than that found in the report on the Western country. However, this is not surprising since BMI values in Asian populations are lower than those in Western populations. To obtain additional BMI-related findings from patients with much higher BMI values (*e.g.* ≥30), further studyies are needed.

In conclusion, both a higher and lower BMI affects the prognosis of UUTUC treated with radical nephroureterectomy. The significant association between higher BMI and risk of death from UUTUC is seen in the male subset, while that between lower BMI and risk of death from UUTUC is seen in the female subset. Further evaluation is required in order to interpret the inverse association between the male and female subsets.

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Received June 29, 2014
Revised July 29, 2014
Accepted July 30, 2014