Optimal body mass index cut-point for predicting recurrence-free survival in patients with non-muscle-invasive urothelial carcinoma of bladder

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Abstract. In Japanese patients with non-muscle-invasive urothelial carcinoma of the bladder, the impact of body mass index (BMI) on recurrence following transurethral resection of bladder tumor (TURBT) is unclear. The present study retrospectively examined data collected from 50 patients diagnosed with primary urothelial carcinoma of the bladder (pTa, pTis, and pT1) who had previously undergone TURBT surgery. Two BMI cut-off points for predicting disease recurrence were evaluated: i) A threshold generated through receiver operating characteristic (ROC) curve analysis; ii) the World Health Organization BMI index (24 kg/m^2) for overweight status in Japanese populations. Univariate and multivariate analyses were applied to assess individual variables (BMI included) and the effect they had on recurrence-free survival (RFS). Median RFS and BMI values of 19.72 months (range, 3.13-72.13 months) and 23.37 kg/m^2 (range, 14.72-36.84 kg/m^2), respectively, were recorded. In multivariate analyses, higher continuous BMI was significantly associated with shorter RFS (P=0.019). Based on a ROC-generated BMI cut-off point (23.4 kg/m^2), patients were ranked with either a high (≥23.4 kg/m^2) or low (<23.4 kg/m^2) BMI status. Multivariate analysis indicated that BMI values >23.4 kg/m^2 were significantly associated with shorter RFS (P=0.028). Intravesical Bacillus Calmette-Guérin treatment and history of upper-tract urothelial carcinoma were also independently associated (P=0.044 and P=0.010, respectively). However, BMI values >24 kg/m^2 (customary cut-off point) had no significant impact on RFS (P=0.066). Thus, a higher BMI status was revealed to be independently predictive of shorter RFS in Japanese patients undergoing TURBT for urothelial carcinoma of the bladder. A greater number of samples are required in order to determine optimal BMI cut-off points in Japanese patients and to investigate whether weight reduction intervention may improve prognosis.

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Introduction

Bladder cancer is a common cancer worldwide, ranking seventh most common cancer in men and the seventeenth in women across the world (1). In Japan, however, bladder cancer ranks fifth in men and the sixteenth in women (2). To assign risk, such tumors are grouped as either muscle-invasive or non-muscle-invasive disease. Transurethral resection of bladder tumor (TURBT) is standard therapy for non-muscle-invasive bladder cancer (NMIBC) (3,4). Because 5-year recurrence rates are high, ranging from 31 to 78% (5), patients should be followed closely after treatment.

Prior investigations of NMIBC have identified a number of prognostic determinants for gauging recurrences of bladder cancer, particularly pathologic features (4) and various biochemical markers (i.e., growth factors) expressed within tumors (6). However, a potential correlation between body mass index (BMI) in patients treated for bladder cancer and disease recurrence after TURBT has not been rigorously examined.

The BMI reflects bodily weight-to-height proportion (weight in kg/height in m^2) and is linked to health risks in many populations (7). Studies of large populations have shown that in patients with muscle-invasive bladder cancer who undergo radical cystectomy, BMI-determined obesity status constitutes a risk factor for recurrence (8-10) and cancer-specific mortality (9-11). However, the prognostic significance of BMI in patients with NMIBC subjected to TURBT has received little attention. Two studies have been performed in US populations (12,13), and one in a Chinese population (14), but none has addressed the Japanese to date.

In this study, we examined the impact of BMI on clinicopathological parameters, including recurrence-free survival (RFS) in pTa, pTis and pT1 stages of bladder cancer, investigating both continuous and categorical BMI values. With respect to categorical BMI values, our goal was to determine

an optimal cut-point. We also assessed the BMI cut-point established by the World Health Organization (WHO) for health risk in Japanese populations (7).

Materials and methods

Study design and patient population. Through retrospective review, we examined clinical data collected from 68 patients whose initial treatment for primary urothelial carcinoma of the bladder was TURBT. All procedures took place at the Tochigi Medical Center Shimotsuga (Tochigi, Japan) between January 2011 and February 2016. A total of 18 patients were subsequently excluded: Two (one man, one woman) given best supportive care upon diagnosis, without further measures (cystoscopy or TURBT); two (both men) opting for radical cystectomy after initial TURBT; 10 (six men, four women) followed postoperatively for <6 months; one man whose pathology specimen yielded insufficient data; and three patients demonstrating pT2 bladder cancer microscopically. Ultimately, 50 patients were selected for evaluation (Fig. 1).

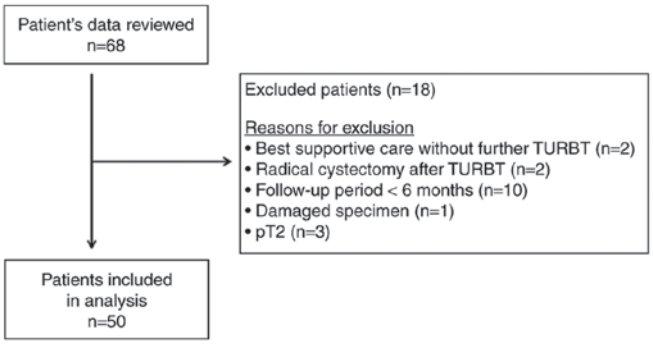

Figure 1. Flowchart of patient selection and exclusion criteria. TURBT, transurethral resection of bladder tumor.

Clinicopathological characteristics. Assessment of patient metadata was undertaken, focusing on gender; age and BMI at first TURBT; risk factors for developing bladder cancer, including smoking status (whether ever-smoker [current or former] or never-smoker) (15), occupational exposures [aromatic amines or polycyclic aromatic hydrocarbons (yes/no)] (16), prior treatment with cyclophosphamide (yes/no) (17), or lower abdominal irradiation [preceding the diagnosis of bladder cancer (yes/no)] (18), past history of upper urinary tract carcinoma (yes/no) (19); and gross/microscopic features of tumors (3), specifically histologic grade (papillary urothelial neoplasm of low malignant potential [PUNLMP], low- or high-grade carcinoma) stipulated by 2004 WHO criteria (20), tumor multicentricity, maximal tumor size (<3 vs. ≥3 cm), clinical T stage (pTa, pTis, or pT1), and histologically confirmed concomitant carcinoma *in situ* (CIS) (yes/no). In each patient, BMI (weight in kg/height in m^2) was calculated and recorded preoperatively.

Follow-up after TURBT. Patients were monitored up every 3-6 months in the first few years after initial TURBT and then every 6-12 months if no recurrences developed, routinely performing urinary cytology and cystoscopy. Biopsies were taken of any suspected recurrent lesions. Recurrence was defined as histologically verified urothelial carcinoma involving any site within the bladder. RFS was defined as the time interval between inital TURBT and first recurrence.

Statistical analysis. We investigated continuous and categorical BMI values, using two separate BMI thresholds: i) A receiver operating characteristic (ROC) curve cut-point and ii) a cut-point of 24 kg/m^2, set by the WHO to reflect overweight status in Japanese populations (7). Categorical BMI values <24 and ≥24 kg/m^2 corresponded with normal and overweight states, respectively. Although the WHO has also established a BMI cut-point of 29.0 kg/m^2 for obesity in the Japanese (7), the present study cohort included too few qualifying subjects (n=4), who were subsequently considered overweight in our analysis. Based on the ROC-generated BMI cut-point, recruited patients were grouped as higher or lower BMI for purposes of comparison.

The Mann-Whitney U test was applied to assess continuous variables, using Fisher's exact test for categorical variables, and comparison of RFS among categorical BMI subsets was achieved via log-rank test. Risk of recurrence was estimated using univariate Cox regression analysis, based on continuous and categorical BMI values. In the absence of recurrence, patients were censored at date of last follow-up exam or at time of death. To assess the relation between BMI and RFS, the multivariate Cox proportional hazard model was engaged. Categorical and continuous BMI values were the main explanatory variables, adjusting for potential confounders through backward stepwise selection.

All P-values were two-sided, setting statistical significance at $P<0.05$. Assorted standard software packages, including GraphPad Prism v7.00 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS statistical software v24.0 [IBM Corp., Armonk, NY, USA] were used to generate graphs and conduct statistical analyses.

Ethical approval. This study was conducted in full accordance with the World Medical Association Declaration of Helsinki and was independently reviewed and approved by the Ethics Committee of Tochigi Medical Center Shimotsuga. Patients were not solicited for informed consent, given the retrospective nature of this study. All patient data were processed in anonymity and de-identified prior to analysis.

Results

Clinicopathological characteristics of patient population. Clinicopathologic characteristics of 50 study participants (male: 33, 66.0%; female: 17, 34.0%), all of whom were Japanese, are shown in Table I. Median age was 73.0 years (range, 53-94 years), and the median observation period was 38.55 months (range, 7.93-74.47 months). Although 25 patients (50.0%) remained recurrence-free, recurrences developed in the other 25 patients during the observation period. The median overall RFS was 19.72 months (range, 3.13-72.13 months), and the median BMI value was 23.37 kg/m^2 (range, 14.72-36.84 kg/m^2). Ever-smokers (current or former) and never-smokers totaled 23 (46.0%) and 27 (54.0%), respectively. Only two patients (4.0%) had histories

Table I. Baseline patient characteristics (n=50).

Variable	Total no.
No. of patients	50
Observation period, months; median (range)	38.55 (7.93-74.47)
Recurrence	
Yes	25 (50.0%)
No	25 (50.0%)
Recurrence-free survival, months; median (range)	19.72 (3.13-72.13)
Age, years; median (range)	73 (53-94)
BMI, kg/m^2; median (range)	23.37 (14.72-36.84)
Sex	
Male	33 (66.0%)
Female	17 (34.0%)
Smoking status	
Current/former	23 (46.0%)
Never	27 (54.0%)
History of upper urinary tract carcinoma	
Yes	2 (4.0%)
No	48 (96.0%)
Intravesical Bacillus Calmette-Guérin	
Yes	6 (12.0%)
No	44 (88.0%)
Exposure to aromatic amines/hydrocarbons	
Yes	0 (0%)
No	50 (100%)
Treatment with cyclophosphamide	
Yes	0 (0%)
No	50 (100%)
Irradiation of lower abdomen	
Yes	0 (0%)
No	50 (100%)
Tumor multicentricity	
Yes	23 (46.0%)
No	27 (54.0%)
Tumor size	
≥3 cm	6 (12.0%)
<3 cm	44 (88.0%)
Histologic grade	
PUNLMP	0 (0%)
Low	36 (72.0%)
High	14 (28.0%)
T stage	
pTis	1 (2.0%)
pTa	35 (70.0%)
pT1	14 (28.0%)
Concomitant CIS	
Yes	3 (6.0%)
No	47 (94.0%)

BMI, body mass index; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*.

of upper-tract urothelial carcinoma, whereas 48 (96.0%) had no such histories prior to diagnosis of bladder cancer. Forty-four patients (88.0%) had never received intravesical Bacillus Calmette-Guérin (BCG) instillation after TURBT, whereas six patients (12.0%) had done so. None of the selected patients were exposed to cyclophosphamide treatment, lower abdominal irradiation, or occupational use of aromatic amines or polycyclic aromatic hydrocarbons. In terms of multicentricity, nearly half of all patients (23/50, 46.0%) had multiple lesions (single tumors: 27/50, 54%). Also, tumors in most instances (44/50, 88.0%) were small-sized (<3 cm), although six patients (12.0%) had sizeable growths (≥3 cm). No patient was diagnosed with PUNLMP (low-grade carcinoma: 36/50, 72.0%; high-grade carcinoma: 14/50, 28.0%). Thirty-five patients (70.0%) were staged as pTa and one patient (2.0%) as pTis. Hence, 36 patients (72.0%) had non-invasive tumors (pTa/pTis), the remaining 14 (28%) exhibiting superficial invasion (pT1). Concomitant CIS was identified in 3 patients (6.0%). There were no instances of nodal or distant-organ metastasis upon initial presentation and during the follow-up period.

Univariate and multivariate analyses of continuous BMI in predicting RFS. Univariate Cox proportional hazards analysis indicated that continuous BMI and RFS were unrelated (hazard ratio [HR]=1.069, 95% CI: 0.966-1.183; P=0.194) (Table II), although a history of upper-tract urothelial carcinoma did show significance (HR=4.802, 95% CI: 1.086-21.24; P=0.039). In multivariate analysis, higher continuous BMI values were significantly associated with shorter RFS (HR=1.138, 95% CI: 1.021-1.268; P=0.019) (Table II), as were intravesical BCG treatment (HR=3.512, 95% CI: 1.085-11.36; P=0.036) and history of upper-tract urothelial carcinoma (HR=17.08, 95% CI: 2.857-102.1; P=0.002).

Optimal BMI cut-point determination. ROC analysis to determine an optimal BMI cut-point for recurrence is graphically depicted in Fig. 2. The Youden index peaked at BMI=23.44 kg/m^2, with an area under the curve (AUC) of 0.584 (95% CI: 0.421-0.747). Sensitivity and specificity were equivalent (64% each). Thus, a BMI of 23.4 kg/m^2 served as optimal cut-point, allowing the grouping of participants by BMI status (higher, ≥23.4 kg/m^2; lower, <23.4 kg/m^2).

Univariate and multivariate analyses of BMI cut-point (higher vs. lower) in predicting RFS. Clinicopathologic features of the cohort are summarized by categorical BMI grouping (higher vs lower) in Table III, showing a well-balanced distribution (P>0.05). In Fig. 3A, Kaplan-Meier estimates of RFS are plotted according to BMI status (higher vs lower). Median RFS intervals in patients of higher and lower BMI groups were 19.4 months (95% CI: 7.47-NA) and NA (95% CI: 17.2-NA), respectively (P=0.084, log-rank test). Multivariate Cox proportional hazards analysis indicated that higher (vs. lower) BMI was significant (HR=2.603, 95% CI: 1.110-6.100; P=0.028) in terms of RFS (Table IV). Intravesical BCG treatment (HR=3.256, 95% CI: 1.032-10.27; P=0.044) and history of upper-tract urothelial carcinoma (HR=7.931, 95% CI: 1.651-38.11, P=0.010) also showed significance in the continuous BMI model.

Table II. Univariate and multivariate analyses of continuous BMI in predicting recurrence-free survival.

	Univariate analysis	Multivariate analysis	
Variable	P-value	HR (95% CI)	P-value
Age (years)	0.316		
Continuous BMI (kg/m^2)	0.194	1.138 (1.021-1.268)	0.019
Sex			
Male	0.489		
Female	-		
Smoking status			
Current/former	0.569		
Never	-		
Intravesical BCG			
Yes	0.175	3.512 (1.085-11.36)	0.036
None	-	Reference	-
Tumor multiplicity			
Multiple	0.234		
Single	-		
Tumor size			
≥3 cm	0.760		
<3 cm	-		
T stage			
pT1	0.664		
pTa/pTis	-		
Tumor grade			
High-grade	0.670		
Low-grade	-		
Concomitant CIS			
Yes	0.223	4.054 (0.860-19.10)	0.077
None	-	Reference	-
History of upper urinary tract carcinoma			
Yes	0.039	17.08 (2.857-102.1)	0.002
None	-	Reference	-

BMI, body mass index; HR, hazard ratio; CI, confidence interval; BCG, Bacille Calmette-Guerin; CIS, carcinoma *in situ*.

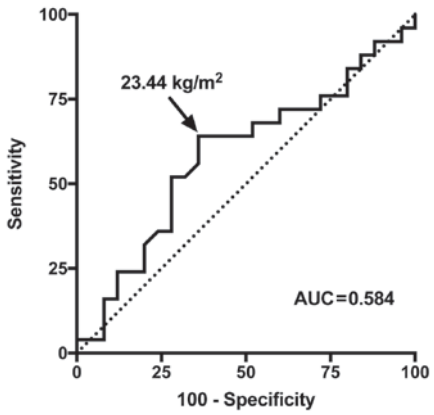

Figure 2. Receiver operating characteristic curve determining the optimal body mass index cut-off point for predicting the risk of non-muscle-invasive bladder cancer recurrence. AUC, area under the curve.

Univariate and multivariate analyses of categorical BMI (normal vs. overweight) in predicting RFS. In Table V, clinicopathologic features of the cohort are shown by categorical BMI status (normal vs. overweight), using the customary BMI cut-point of 24 kg/m^2. Overall, 62.0% (31/50) qualified as normal BMI (<24.0 kg/m^2), whereas 38.0% (19/50) were considered overweight (BMI ≥24.0 kg/m^2). Again, group distributions were well balanced (P>0.05). Kaplan-Meier estimates of RFS were plotted by BMI status in Fig. 3B. Median RFS intervals in patients stratified by categorical BMI status (normal vs. overweight) were 41.6 months (95% CI: 32.0-NA) and 11.9 months (95% CI: 5.47-NA), respectively (P=0.125, log-rank test) (Fig. 3B). In multivariate Cox proportional hazards analyses, overweight BMI status showed no significant association with RFS (HR=2.136, 95% CI 0.950-4.800; P=0.066) (Table VI). However,

Table III. Characteristics of patient population (n=50) demonstrated by categorized BMI (higher versus lower).

Variable	BMI <23.4 kg/m^2	BMI ≥23.4 kg/m^2	P-value
No. of patients (%)	26 (52.0%)	24 (48.0%)	
Recurrence			0.156
Yes	10	15	
No	16	9	
Observation period (months)			0.712
Median	37.13	43.50	
Range	13.57-72.13	7.9 -74.47	
Age (years)			0.648
Median	73	75.5	
Range	60-89	53-94	
Sex			0.767
Male	18	15	
Female	8	9	
Smoking status			0.584
Current/former	13	10	
Never	13	14	
History of upper urinary tract carcinoma	1		
Yes	1	1	
No	25	23	
Intravesical BCG			0.669
Yes	4	2	
No	22	22	
Tumor multicentricity			0.584
Yes	13	10	
No	13	14	
Tumor size			1.000
≥3 cm	3	3	
<3 cm	23	21	
T stage			1.000
pTa/pTis	19	17	
pT1	7	7	
Histologic grade			0.352
PUNLMP	0	0	
Low	17	19	
High	9	5	
Concomitant CIS			0.669
Yes	1	2	
No	25	22	

BMI, body mass index; BCG, Bacillus Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*.

history of upper-tract urothelial carcinoma did emerge as an independent prognostic index of RFS (HR=6.664, 95% CI 1.430-31.06; P=0.016).

Table IV. Multivariate Cox regression analyses of factors impacting recurrence-free survival, including categorical BMI (higher vs. lower).

Variable	HR (95% CI)	P-value
Categorical		
BMI (kg/m^2)		
≥23.4	2.603 (1.110-6.100)	0.028
<23.4	Reference	-
Intravesical BCG		
Yes	3.256 (1.032-10.27)	0.044
No	Reference	-
History of upper urinary tract carcinoma		
Yes	7.931 (1.651-38.11)	0.010
No	Reference	-

HR, hazard ratio; CI, confidence interval; BMI, body mass index; BCG, Bacillus Calmette-Guérin.

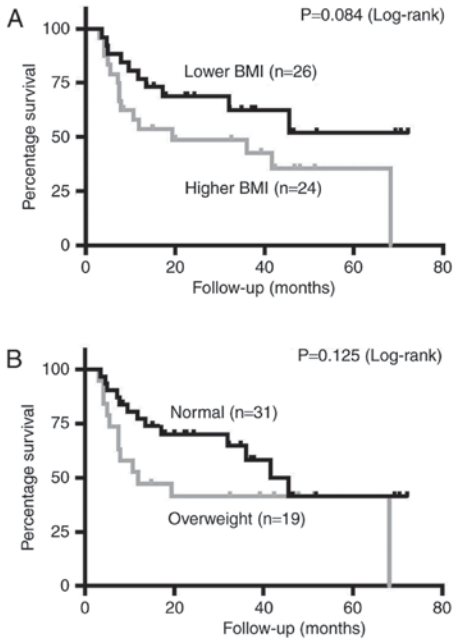

Figure 3. Kaplan-Meier plots of (A) categorical BMI values (normal vs. overweight) to predict recurrence-free survival and (B) categorical BMI values (higher vs. lower) to predict recurrence-free survival. BMI, body mass index.

Discussion

The chief objective of this study was to assess the relation between BMI and RFS in Japanese patients with NMIBC, determining optimal BMI cut-points for gauging the risk of disease recurrence. Through our efforts, we made the following observations: i) Higher continuous BMI values were associated with shorter RFS in Japanese patients with NMIBC; ii) the optimal ROC-generated BMI cut-point (23.4 kg/m^2) for predicting recurrences differed from thresholds for overweight and obese states established by the WHO (7); and iii) RFS

Table V. Characteristics of patient population (n=50) demonstrated by categorized BMI (normal vs. overweight).

Variable	BMI <24 kg/m^2	BMI ≥24 kg/m^2	P-value
No. of patients (%)	31 (62.0%)	19 (38.0%)	
Recurrence			0.244
Yes	13	7	
No	18	12	
Observation period (months)			0.772
Median	37.13	42.40	
Range	7.93-72.13	8.43-74.47	
Age (years)			0.200
Median	70	77	
Range	60-89	53-94	
Sex			0.767
Male	21	12	
Female	10	7	
Smoking status			0.773
Current/former	15	8	
Never	16	11	
History of upper urinary tract carcinoma			1
Yes	1	1	
No	30	18	
Intravesical BCG			1
Yes	4	2	
No	27	17	
Tumor multicentricity			1
Yes	14	9	
No	17	10	
Tumor size			0.661
≥3 cm	3	3	
<3 cm	28	16	
T stage			0.750
pTa/pTis	23	13	
pT1	8	6	
Histologic grade			1
PUNLMP	0	0	
Low	22	14	
High	9	5	
Concomitant CIS			0.549
Yes	1	2	
No	30	17	

BMI, body mass index; BCG, Bacillus Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*.

Table VI. Multivariate Cox regression analyses of factors impacting recurrence-free survival, including categorical BMI (normal vs. overweight).

Variable	HR (95% CI)	P-value
Categorical BMI (kg/m^2)		
≥24	2.136 (0.950-4.800)	0.066
<24	Reference	-
Intravesical BCG		
Yes	2.772 (0.902-8.521)	0.075
No	Reference	-
History of upper urinary tract carcinoma		
Yes	6.664 (1.430-31.06)	0.016
No	Reference	-

HR, hazard ratio; CI, confidence interval; BMI, body mass index; BCG, Bacillus Calmette-Guérin.

was significantly shorter in this setting at higher BMI values (≥23.4 kg/m^2). Thus, continuous BMI values carry significant weight in predicting RFS. However, because continuous BMI is not easily implemented in clinical settings, we determined an optimal BMI cut-point for this purpose. To date, no previous studies on the relation between BMI and recurrence of bladder cancer after TURBT have addressed Japanese populations. To our knowledge, this study is the first to support an association between BMI and RFS in Japanese patients after TURBT treatment of NMIBC.

BMI is an easily calculable measure of bodily weigh-to-height proportion. BMI categorization (i.e., normal, overweight, and obese states) is linked to health risks (7). Associations between BMI and prognosis have already been demonstrated in some malignant tumors, primarily breast and prostate cancers. Patients with high BMIs at the time of breast cancer discovery have significantly increased risk of distant recurrence (21,22) and overall mortality (23). In one particular meta-analysis, higher BMI values were implicated in breast cancer incidence (24). Furthermore, higher BMI showed a significant association with greater incidence of prostate cancer in a US population (25) and higher risk of mortality (26-28). In terms of urothelial carcinoma, stratification by categorical BMI (≥22 vs. <22 kg/m^2) in upper tract lesions of the kidney and ureter proved significantly prognostic of overall survival and cancer-specific survival in Japanese subsets (29).

Most research on the relation between bladder cancer and BMI has involved the prognosis after radical cystectomy in muscle-invasive bladder cancer, linking a BMI ≥30 kg/m^2 with higher risks of disease recurrence in US (8) and French (9) study populations. Another investigation of both US and Japanese cohorts has identified higher continuous BMI as an independent risk factor for 90-day mortality following radical cystectomy (11). By comparison, there are few studies on the prognostic impact of BMI after TURBT in patients with NMIBC. In one US-based report, obesity (BMI ≥30 kg/m^2) was found to correlate with risk of recurrent/progressive disease, cancer-specific mortality, and all-cause mortality in patients with pT1 bladder cancer (12). Unfortunately, analysis of progression-free survival was

not feasible in our cohort, owing to so few events (n=4); and cancer-specific mortality was non-calculable because no patients in the present study had died during follow-up monitoring. Nevertheless, another study conducted in the US has shown that overweight status (BMI >24.9 kg/m^2) has a significant adverse effect on RFS among continuing smokers (13). Likewise, higher BMI has emerged as an independent predictor of shorter RFS in Chinese patients with NMIBC, using 24 and 28 kg/m^2 as respective cut-points for overweight status and obesity (14). These cut-points were adjusted for the study population and differed from those typically assigned to Western subjects. The cut-points of BMI for a health risk can be different between Asian and Western populations because they have different associations between BMI, percentage of body fat, and health risks (7).

In Japanese populations, the WHO has established BMI cut-points of 24 kg/m^2 for overweight status and 29 kg/m^2 for obesity (7). However, our analysis failed to implicate this threshold for overweight status (BMI ≥24.0 kg/m^2) as a significant factor in RFS (P=0.066). We did not evaluate the other cut-point (BMI ≥29.0 kg/m^2) because so few of patients (n=4) qualified as obese on this basis. Our independently generated optimal BMI cut-point differed from the above WHO standard thresholds for overweight and obese states (7). It may well be that a disease-specific BMI cut-point is needed for prognostic risk stratification in NMIBC, rather than conventional BMI thresholds (i.e., normal, overweight, or obese). Consistent with earlier studies of Chinese (14) and US populations (12,13), outcomes herein provide evidence that higher BMI is associated with increased risk of disease recurrence in Japanese patients with NMIBC.

It is also apparent that fluctuations in BMI may similarly influence the prognosis of cancer patients. In instances of triple-negative breast cancer, patients considered obese (BMI ≥28.0 kg/m^2) before diagnosis or those achieving weight loss of ≥5% at 18 or 36 months post-diagnosis displayed greater risk of overall mortality, disease recurrence, and disease-specific mortality (30). In patients with early-stage breast cancer, instituting a low-fat diet has resulted in weight reduction and a comparatively lower recurrence rate (31). What's more, physical activity after discovery of cancer is associated with better cancer-specific and overall survival in patients with early-stage breast, prostate, or colorectal cancer (32-36). In bladder cancer, one meta-analysis reported that physical exercise was associated with decreased risk of bladder cancer (37). Given that changing BMI and prognosis are related in certain malignancies (such as breast or prostate cancer), weight loss through physical activity after TURBT may prove beneficial, lowering BMI values below the recurrence cut-point and reducing recurrence rates in in those patients with excessive bodily fat.

The mechanism underlying the observed interrelation of BMI and RFS in patients with bladder cancer remains unclear. Patients with metabolic syndrome (MeS) and higher BMI values than patients without MeS presented with higher T stage and histologic tumor grades (38). In the current study, none of pathologic features of tumors were associated with categorical BMI (normal vs. overweight or higher vs lower). Xu *et al* reported that being overweight and obese had different risks on recurrence or progression in NMIBC (14). This difference can be due to different amount of energy intake. Excessive energy may contribute to carcinogenesis because of alterations in the metabolism of endogenous hormones-including sex steroids, insulin, and insulin-like growth factors (39). In breast cancer, adiposity-induced insulin resistance has been cited as the link between BMI and recurrent disease (31). Indeed, an association between overexpression of insulin receptors in the breast cancer cells of obese patients and poor prognosis has been demonstrated (31). One study has shown that high BMI in conjunction with negative expression of progesterone receptors serves as an independent risk factor for breast cancer recurrences in patients treated with adjuvant aromatase inhibitors (40). In muscle-invasive bladder cancer, expression of insulin receptors in tumor-associated blood vessels also has correlated with poor overall and progression-free survival (41). Consequently, assay of plasma obesity-related molecules or evaluation of hormonal receptor expression in bladder tumors may help elucidate the mechanism of tumorigenesis encouraged by higher BMI in patients with bladder cancer.

The current study has several acknowledged limitations. First, our patient sampling was small and originated from a single institution, possibly reflecting selection bias when applied to the Japanese population at large and rendering current outcomes underpowered to identify weak associations. Furthermore, we did not distinguish between overweight and obese states in evaluating BMI. Although the WHO has set a BMI cut-point for obesity in Japan (29 kg/m^2) (7), we had too few obese participants (n=4) to perform survival analysis. A balanced distribution of overweight and obese BMI participants would be needed for precise evaluation of relevant differences.

Another study weakness was a lack of patient data on fat and muscle mass. The BMI does not differentiate between weight attributable to fat or to muscle. One pertinent publication has emphasized that defining obesity solely on the basis of BMI without considering muscle mass creates inaccuracies, although BMI is an easy parameter to measure (42). Finally, the present investigation did not include data on changes in BMI after initial TURBT. Thus, the impact of BMI fluctuations on RFS could not be explored. In Japanese patients with NMIBC, higher BMI showed an associated with shorter RFS. Further studies of larger patient populations are needed to determine optimal BMI cut-points in Japanese patients and investigate whether weight reduction intervention improves prognosis.

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