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ORIGINAL PAPER

Postoperative weight loss followed by radical cystectomy predicts poor prognosis in patients with muscle-invasive bladder cancer

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Abstract

We aimed to investigate the impact of postoperative weight loss following radical cystectomy (RC) on patients' prognoses. RC and urinary diversion were performed in 512 consecutive patients with muscle-invasive bladder cancer at our hospitals between May 1996 and July 2018. Demographic clinical information, pre- and postoperative serum albumin, hemoglobin, and weight were evaluated retrospectively at 1 month. We also evaluated the association of weight loss with complications and overall survival (OS) as estimated using the Kaplan–Meier method and compared using the log-rank test. Risk factors for poor OS were determined by Inverse Probability of Treatment Weighted (IPTW)-adjusted Cox regression analysis. In 385 patients who met the study search criteria, median postoperative weight loss from baseline at 1 week and 1 month was 1.1 (− 1.8%) and 3.2 (− 5.4%) kg, respectively. Patients with significant weight loss (defined as ≥ 7.5% at 1 month) had higher-grade complications within 1 month and had significantly shorter OS than those with weight loss of < 7.5%. Type of urinary diversion, loss of serum albumin, and loss of hemoglobin were not significantly associated with weight loss. IPTW-adjusted Cox regression analysis showed that such significant weight loss was an independent risk factor for poor OS. Weight loss followed by radical cystectomy was significantly associated with poor prognosis in patients with muscle-invasive bladder cancer.

Keywords Cystectomy · Weight loss · Frailty · Survival · Bladder cancer

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Introduction

Radical cystectomy (RC) and urinary diversion remain the gold standard surgical treatment for muscle-invasive bladder cancer (MIBC) [1–7]. Although minimally invasive procedures have been developed [3–5], surgical stress, including blood loss, postoperative complications, and poor nutrition status, are inevitable problems [8, 9]. Of those complications, the impact of postoperative weight loss (WL) on poor prognosis has been reported [10]. Postoperative WL following RC is common. It was reasonable to consider that a highly invasive procedure for potentially frail MIBC patients resulted in remarkable WL and unfavorable outcomes. Previous reports suggested that an acute WL of 5%–10% within 1 month indicated significant malnutrition [11] and a 3%–5% WL within 6 months was a sign of frailty [12, 13]. Another prior study suggested that ≥ 10% WL had a significant impact on poor prognosis [10]. However, few studies are available regarding the impact of postoperative WL on prognosis following RC [10, 14] and the optimal cutoff value for poor prognosis has not been well elucidated. Therefore, we investigated the association of WL following RC with postoperative complications and prognosis.

Materials and methods

Design and ethics statement

This retrospective, multicenter study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethics committee of the Hirosaki University School of Medicine (authorization number, 2018-062). Verbal or written informed consent was obtained from all participants. Pursuant to the provisions of the ethics committee and ethical guidelines in Japan, written consent was not required in exchange for public disclosure of the study information (opt-out approach) in the case of a retrospective and/or observational study using material, such as the existing documentation.

Patient selection and demographics

RC and urinary diversion were performed in 512 consecutive patients with muscle-invasive bladder cancer at our hospitals between May 1996 and July 2018. Exclusion criteria were the presence of metastatic disease preoperatively and no documented weight within 1 month postoperatively. Indications for RC and urinary diversion were determined by the operating surgeon. A perioperative enhanced recovery protocol was not used routinely. Retrospectively evaluated demographic clinicopathologic information included age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), hypertension (HTN), cardiovascular disease (CVD), diabetes mellitus (DM), renal function, clinical stage, and surgical and pathologic outcomes. Renal function was evaluated by estimated glomerular filtration rate (eGFR) before RC using a modified version of the abbreviated Modification of Diet in Renal Disease Study formula for Japanese patients [15]. Pre- and postoperative serum albumin, hemoglobin, and weight at 1 week and 1 month were measured. Tumor stage was stratified in accordance with the Union of International Cancer Control 2009 tumor-node-metastasis classification. Postoperative complications were evaluated by the Common Terminology Criteria for Adverse Events ver. 4.0. Since September 2006, patients have received two to four courses of neoadjuvant chemotherapy (NAC) for the treatment of MIBC, composed of a platinum-based combination regimen with gemcitabine plus cisplatin; gemcitabine plus carboplatin; or methotrexate, vinblastine, adriamycin, and cisplatin. Regimens were selected based on guidelines regarding eligibility for the proper use of cisplatin and overall patient status.

Outcomes

An optimal cutoff value for poor overall survival (OS) was determined by the area under the receiver operating characteristics (ROC) curve. We evaluated the association of postoperative WL with complications and OS.

Statistical analysis

Data were analyzed statistically using SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA), GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or the χ^2 test. Quantitative variables were expressed as a mean with standard deviation or a median with interquartile range (IQR). Intergroup differences were analyzed by Student's *t*-test or the Mann–Whitney *U* test. OS stratified by WL was estimated using the Kaplan–Meier curve and log-rank test. Risk factors for poor prognosis were determined by multivariate Cox regression analysis (model-1). In addition to model-1, we used Inverse Probability of Treatment Weighted (IPTW)–adjusted Cox regression analysis to evaluate the impact of WL on OS (model-2). The IPTW model reweighted affected and unaffected groups to mimic a propensity score-matched population [15–17]. A hazard ratio (HR) with 95% confidence interval (95% CI) was calculated after controlling for potential confounders, including patient demographics

and clinicopathologic tumor variables. Variables included in model-1 were age, sex, NAC, complications, type of urinary diversion, pathologic risk (pT3-4, lymphovascular invasion [LVI]+ or pN+), and WL. Model-2 included factors in model-1 plus BMI, eGFR, and operative time.

Results

Baseline characteristics

Of 385 patients (median age, 69 years; IQR, 62–74) who met the search criteria in this study, 255 (66%), 41 (11%), and 89 (23%) underwent orthotopic ileal neobladder construction, ileal conduit diversion, and ureterocutaneostomy, respectively. NAC was given in 268 patients (70%). Grades 2 and ≥ 3 postoperative complications were observed in 78 (20%) and 17 (4.4%) patients, respectively. Median changes in postoperative serum albumin, hemoglobin, and weight from baseline at 1 week and 1 month were 1.0 (− 23%) and 0.5 (− 10%), 2.7 (− 18%) and 2.1 (− 15%), and 1.1 (− 1.8%) and 3.2 (− 5.4%) kg, respectively (Fig. 1a).

Optimal cutoff value and patient stratification

ROC analysis showed that WL ≥ 7.5% at 1 month was the optimal cutoff value to define significant WL. We stratified and compared patients who had a WL of ≥ 7.5% (group 1) and < 7.5% (group 2). There were significant differences in BMI, preoperative eGFR, operative time, and grade ≥ 2 postoperative complications between the two groups at 1 month (Table 1). WL was not significantly different between patients undergoing orthotopic ileal neobladder construction and other procedures (ileal conduit and ureterocutaneostomy; Fig. 1b). Group 1 patients had more high-grade complications (grade ≥ 2) within 1 month (19% vs. 40%, $P < 0.001$; Fig. 1c). The rates of changes in serum albumin (Fig. 1d) and hemoglobin (Fig. 1e) at 1 week and 1 month were not significantly different between the two groups. However, the rates of weight change were significantly different (Fig. 1f).

Weight loss and mortality

Group 1 patients had a significantly shorter OS than did those in group 2 (5-year OS, 78% and 67%, respectively;

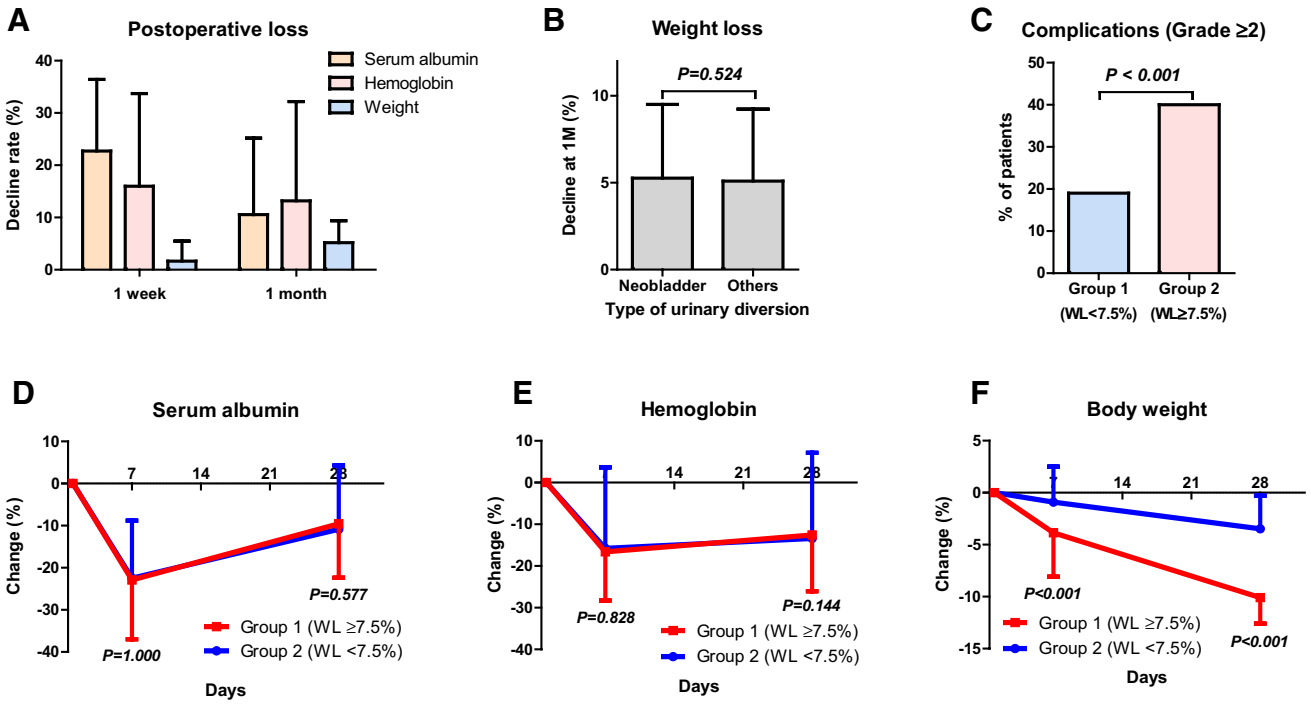

Fig. 1 Trends in the postoperative parameters. Median changes in postoperative serum albumin, hemoglobin, and weight from baseline at 1 week and 1 month were 1.0 (− 23%) and 0.5 (− 10%), 2.7 (− 18%) and 2.1 (− 15%), and 1.1 (− 1.8%) and 3.2 (− 5.4%) kg, respectively (**a**). Weight loss (WL) was not significantly different between patients who underwent orthotopic ileal neobladder construction and other procedures (ileal conduit and ureterocutaneostomy) (**b**). Patients with WL ≥ 7.5% had more high-grade complications (grade ≥ 2) within 1 month (19% vs. 40%, $P < 0.001$) (**c**). The rates of changes in serum albumin (**d**) and hemoglobin (**e**) at 1 week and 1 month were not significantly different between the two WL groups, while the rates of weight change were significantly different (**f**)

Table 1 Background of patients

	Group 1 (weight loss ≥ 7.5%)	Group 2 (weight loss < 7.5%)	*P* value
n	101	284	
Median age (years (IQR))	67 (61–72)	70 (63–75)	0.198
Sex (male) (*n*)	80 (86%)	209 (77%)	0.047
ECOG PS ≥ 1 (*n*)	4 (4.0%)	5 (1.8%)	0.250
Body mass index (kg/m^2 (IQR))	23.5 (22.2–25.8)	22.5 (20.6–24.9)	0.006
Hypertension (HTN) (*n*)	29 (29%)	89 (31%)	0.623
Diabetes mellitus (DM) (*n*)	20 (20%)	40 (14%)	0.201
Cardiovascular disease (CVD) (*n*)	14 (14%)	35 (12%)	0.729
preoperative eGFR, ml/min/1.73 m^2 (IQR)	70 (59–86)	68 (55–77)	0.003
Neoadjuvant chemotherapy (NAC) (*n*)	71 (70%)	197 (69%)	0.861
Clinical stage (*n*)			
cT3-4	56 (55%)	134 (47%)	0.154
cN+	8 (7.9%)	21 (7.4%)	0.829
Surgical outcomes			
Urinary diversion (Ileal neobladder) (*n*)	64 (63%)	191 (67%)	0.540
Postoperative complications (grade ≥ 2)	40 (40%)	55 (19%)	< 0.001
Blood loss (g (IQR))	1150 (642–1720)	1000 (668–1739)	0.964
Operative time (min)	306 (261–369)	282 (239–342)	0.003
Pathological outcomes (*n*)			
Tumor grade (high)	81 (80%)	235 (83%)	0.550
pT3 or 4	31 (33%)	69 (25%)	0.132
pN+	8 (7.9%)	30 (11%)	0.561
Lymphovascular invasion (LVI)+	37 (37%)	83 (29%)	0.171
Median follow-up (months (IQR))	46 (15–76)	71 (24–113)	

$P < 0.001$; Fig. 2a). In a multivariate Cox regression analysis, age, NAC, pathologic high-risk, and WL ≥ 7.5% at 1 month were selected as independent risk factors for poor OS (Fig. 2b, model-1 in Table 2). In IPTW-adjusted Cox regression analysis, WL ≥ 7.5% at 1 month was an independent risk factor for poor OS (HR, 2.13, $P < 0.001$, model-2 in Table 2).

Discussion

We demonstrated the association of oncologic outcomes with WL following RC in MIBC patients. Our results suggested that the median WL was 5.4% at 1 month. WL of ≥ 7.5% at 1 month was associated with a higher rate of

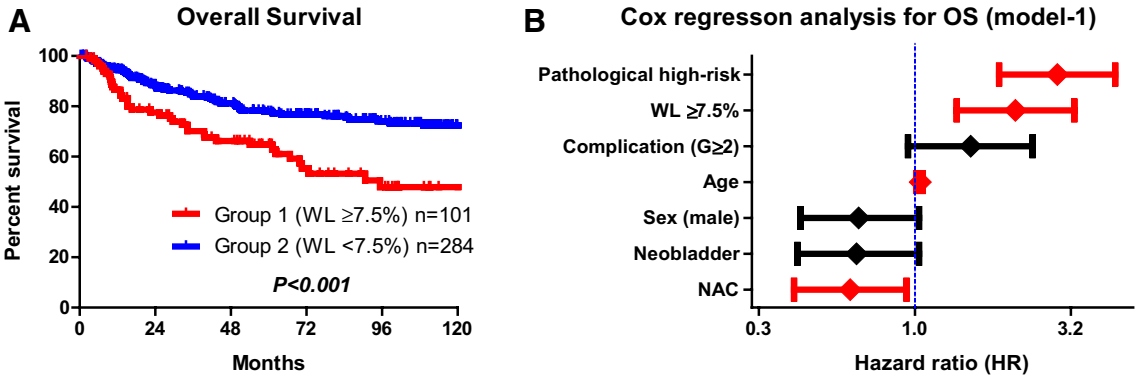

Fig. 2 OS stratified by the weight loss (WL). Group 1 patients had significantly shorter OS than did those in group 2 ($P < 0.001$, **a**). 5-year OS in groups 1 and 2 was 78% and 65%, respectively. On multivariate Cox regression analysis (model-1), age, NAC, pathologic high-risk, and WL ≥ 7.5% at 1 month were selected as independent factors for poor OS (**b**)

Table 2 Multivariate (model-1) and IPTW-adjusted (moel-2) Cox regression analyses for overall survival

	Factor	*P* value	HR	95% CI
Model-1				
Age	Continuous	0.002	1.04	1.01–1.06
Sex	Male	0.068	0.65	0.42–1.03
Neoadjuvant chemotherapy	Underwent	0.024	0.62	0.41–0.94
Type of urinary diversion	Ileal neobladder	0.066	0.66	0.43–1.03
Postoperative complication	Grade ≥ 2	0.081	1.51	0.95–2.38
Pathological high-risk	pT3-4, or LVI+, or pN+	< 0.001	2.86	1.86–4.38
Weight loss followed by RC	≥ 7.5%	0.001	2.10	1.36–3.24
Model-2				
Weight loss followed by RC	≥ 7.5%	< 0.001	2.13	1.36–3.34

IPTW: Inverse Probability of Treatment Weighted. Variables included in the model-1 was age, sex, NAC, complications, type of urinary diversion, pathological risk (pT3-4, lymphovascular invasion + or pN+), and weight loss. The model-2 included factors in model-1 plus BMI, eGFR, and operative time

complications and poor OS than WL of < 7.5%. We also noted that the influences of type of urinary diversion, preoperative serum albumin, and hemoglobin on WL were not significant. Although postoperative WL is important in the prognosis of patients after major surgery, few studies have evaluated its impact on prognosis in MIBC patients after RC [10, 14]. McDonald et al. [10] suggested that mean WL following RC was − 7.8% at 1 month and a WL of ≥ 10% was significantly associated with decreased 5-year survival rates after RC. However, there were differences in mean WL between the studies, which might be due to the body size gap that exists between Asian and Western populations. The difference in mean BMI may demonstrate the body size difference between Western (28.1 ± 4.4) and Asian (23.1 ± 3.3) populations in the previous study. Based on this hypothesis, we determined the optimal cutoff value for poor OS in our study to be ≥ 7.5% and found a significant association between WL and poor prognosis. This suggested that the cutoff value needs modification for each nation. In addition, the impact of WL on urinary diversion was not identical. The rate of patients with an ileal neobladder was higher in our study (66%) compared to the previous report (23.9%). Further study is necessary to address these differences and the association of oncologic outcomes with WL following RC in MIBC patients.

Our results showed that the prognosis in patients with ≥ 7.5% WL was significantly poorer than in those with < 7.5% WL based on multivariate analysis as well as in the pathologic high-risk (model-1). Conversely, NAC use was associated significantly with prolonged OS (HR, 0.62, $P = 0.024$), which was consistent with the findings of our previous studies [18–20]. However, the small number of patients with ≥ 7.5% WL ($n = 101$) resulted in underpowered statistics and prevented potential conclusions. To improve this problem, we used the IPTW-adjusted multivariate analysis (model-2) for OS, which revealed a significant association (HR, 2.13; $P < 0.001$) that was similar to model-1. A multicenter prospective study is necessary to validate our observation.

We noted that postoperative serum albumin and hemoglobin levels were not associated with WL following RC. The clinical implication of these levels has not been well elucidated, although the preoperative serum albumin value was well documented [14, 21]. We hypothesized that postoperative serum albumin and/or hemoglobin levels may have contributed to nutritional status and resulted in WL. However, our results showed no difference in serum albumin and hemoglobin levels between the two WL groups. A potential surrogate marker for WL may be the number of calories consumed and nutritional balance following RC for a month, but this is not feasible in daily practice. Although further study is necessary to address these issues, our results suggested that other parameters are necessary to predict candidates for significant WL and poor prognosis following RC.

Frailty is a key factor for postoperative loss of weight. WL is included in the Freid's Frailty phenotype criteria as well as exhaustion, physical activity, gait speed, and grip strength [13, 22]. Several studies suggested that frailty is a predictor of surgical outcomes following RC, including postoperative complications and poor prognosis [13, 23, 24]. However, measuring frailty is challenging because of heterogeneity in aging and disagreement between chronologic and biological ages [22] and no clear evidence supports the direct association between postoperative WL and frailty. Our ongoing study evaluating preoperative frailty (UMIN000025057) will address the association of preoperative frailty with postoperative WL following RC. A comprehensive geriatric assessment including multiple domains of health may improve patient outcomes through possible interventions, such as a prehabilitation [25, 26].

The prevention of WL following RC is an important target for interventions. Multimodal prehabilitation and/or enhanced recovery protocols may lead to acceptable outcomes, as these approaches are associated with a lower

postoperative complication rate, earlier restoration of functional status, and shorter length of stay [27–29]. However, evidence relating to the effects of exercise for RC is very limited, as not all randomized controlled trials of pre- and postoperative rehabilitation programs for RC pathways improved short-term outcomes [26]. In addition, the impact of these protocols on OS remains unclear because many studies focused on short-term outcomes, such as early mobilization, time required to perform activities of daily living, and complications [27, 30]. Therefore, the clinical impact of pre- and postoperative rehabilitations following RC remains unclear [26], and further studies are necessary to optimize these strategies to improve prognosis.

Several limitations of our study must be acknowledged. First, we were unable to control for selection bias and other unmeasurable confounders due to the retrospective study design. This prevented us from reaching definitive conclusions regarding the impact of WL following RC on oncologic outcomes. Second, our results could not be applied to those of other nations under different medical systems because of the regional bias present in Japan. Nonetheless, our study supported the importance of WL following RC as a potential prognostic marker. Further study is necessary to address the impact of WL following RC on oncologic outcomes.

Conclusion

Postoperative WL of $\geq 7.5\%$ following RC was significantly associated with poor prognoses in patients with MIBC.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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