Review Article

Impact of sarcopenia in bladder preservation therapy for muscle-invasive bladder cancer patients: a narrative review

Hiroshi Fukushima[1]^, Fumitaka Koga[2]^

[1]Department of Urology, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan; [2]Department of Urology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku, Tokyo, Japan

Contributions: (I) Conception and design: H Fukushima; (II) Administrative support: H Fukushima; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: H Fukushima; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Hiroshi Fukushima, MD, PhD. Department of Urology, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. Email: fukuuro@tmd.ac.jp.

Background and Objective: Muscle-invasive bladder cancer (MIBC) is a biologically aggressive disease and its prognosis is poor. Radical cystectomy (RC) with urinary diversion and lymph node dissection is the gold standard treatment for MIBC patients. Accumulating evidence indicates that sarcopenia, the degenerative and systemic loss of skeletal muscle mass, is a significant predictor of higher rates of mortality and perioperative complications following RC. Recently, bladder preservation therapy has been offered as an alternative in appropriately selected MIBC patients who desire to preserve their bladders and those unfit or unwilling for RC. Here, we performed a narrative review on the impact of sarcopenia on oncological outcomes and complication rates in MIBC patients treated with bladder preservation therapy.

Methods: A literature review was performed using the PubMed and Scopus databases.

Key Content and Findings: We identified two studies reported the impact of sarcopenia on responses to trimodal therapy and survival outcomes in MIBC patients. Consolidative partial cystectomy was performed in patients who achieved clinical complete response (CR) to trimodal therapy in one of the two studies. In both studies, CR rates to trimodal therapy are comparable between sarcopenic and non-sarcopenic patients. Sarcopenia was not significantly associated with shorter survival after completing bladder preservation therapy in either study. For complication rates of bladder preservation therapy, one study showed equivalent complication rates of consolidative partial cystectomy between sarcopenic and non-sarcopenic patients. In addition, in another small series of trimodal therapy, sarcopenic patients showed a higher rate of complications of trimodal therapy compared with non-sarcopenic patients.

Conclusions: According to the result of our literature review, sarcopenia would not affect responses to trimodal therapy and prognosis in MIBC patients treated with bladder preservation therapy. Although the effect of sarcopenia on complication rates of bladder preservation therapy is inconclusive due to limited evidence, bladder preservation therapy could be a viable alternative option in carefully selected MIBC patients regardless of the presence of sarcopenia.

Keywords: Sarcopenia; frailty; muscle-invasive bladder cancer (MIBC); bladder preservation therapy; trimodal therapy

Submitted May 14, 2022. Accepted for publication Sep 14, 2022.
doi: 10.21037/tau-22-355
View this article at: https://dx.doi.org/10.21037/tau-22-355

^ ORCID: Hiroshi Fukushima, 0000-0001-7548-1580; Fumitaka Koga, 0000-0001-7888-0085.

Introduction

Bladder cancer is the second most common genitourinary malignancy worldwide, with approximately 573,000 new cases and 212,000 deaths from bladder cancer in 2020 (1). Based on the stage, bladder cancer is divided into two categories: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). MIBC is more biologically aggressive than NMIBC and accounts for approximately 25% of all bladder cancer cases. Radical cystectomy (RC) with urinary diversion and lymph node dissection has been the gold standard treatment in MIBC patients (2). However, RC is an invasive and complex procedure and has considerable rates of complications that can cause bowel, urinary, and sexual dysfunctions. Moreover, these functional changes worsen quality of life (QOL) of patients (3). According to a systematic review of perioperative outcomes after robot-assisted RC, a 30-day overall complication rate, major complication rate, and mortality rate were 44%, 11.8%, and 1.6%, respectively (4).

Most MIBC patients are diagnosed beyond the age of 65, indicating that they can have poor general health status, many comorbidities, and frailty (5). Recently, sarcopenia, the degenerative and systemic loss of skeletal muscle mass, has gained interest in the management of cancer-bearing patients as an indicator of frailty (6,7). It can be caused by multiple etiologies such as advanced age, lack of physical activity, poor nutritional status, inflammatory diseases, endocrine disorders, neuromuscular diseases, and malignancies (8). A previous epidemiological study showed a high frequency of sarcopenia in the older population, with 13–24% at 65–70 years and over 50% at 80 years or older (9). The number of sarcopenic population is expected to reach 1.2 billion by 2025 and it will have doubled by 2050 (10). A growing number of studies showed that sarcopenia had a negative impact on prognosis in various cancers including lung or gastrointestinal cancer (11), esophageal cancer (12), gastric cancer (13), head and neck cancer (14) upper tract urothelial cancer (15), prostate cancer (16), and kidney cancer (17). Moreover, sarcopenia is associated with intolerance to cancer treatment and a higher rate of perioperative complications (18,19). For bladder cancer, sarcopenia is a significant predictor of worse cancer-specific survival (CSS) and a higher rate of perioperative complications in patients undergoing RC, suggesting that sarcopenic patients could be potentially unfit for RC (20-23). In addition, sarcopenic patients have poor prognosis in advanced disease treated with an immune checkpoint inhibitor (ICI) (24).

Bladder preservation therapy, which is generally called as 'trimodal therapy' and comprised of transurethral resection of the bladder tumor (TURB), chemotherapy, and radiotherapy, is an alternative therapeutic option in appropriately selected MIBC patients and those unfit or unwilling for RC (2,25). Bladder preservation therapy showed excellent long-term outcomes especially in appropriately selected patients with favorable clinical features such as small, solitary, and non-metastatic diseases, the absence of hydronephrosis, and the absence of extensive carcinoma *in situ* (26-28). Moreover, patients treated with bladder preservation therapy maintain good QOL after treatment (29,30). Given its less invasiveness compared with RC, bladder preservation therapy may be fit for sarcopenic MIBC patients. In this study, we summarized the definitions of computed tomography (CT)-determined sarcopenia and reviewed the literature on the impact of sarcopenia on oncological outcomes and complication rates in MIBC patients treated with bladder preservation therapy. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-355/rc)

Definitions of CT-determined sarcopenia

CT-determined sarcopenia can be easily and objectively evaluated with a high reproducibility (31). Thus, CT scan is generally used in the evaluation of sarcopenia in many clinical studies. To evaluate sarcopenia, the total skeletal muscle area at the third lumbar spinal level is measured using axial CT slices (32,33). The cross-sectional area of the psoas, paraspinal muscles (the erector spinae and quadratus lumborum), and abdominal wall muscles (the transversus abdominus, external and internal obliques, and rectus abdominus) is identified using Hounsfield unit range of –29 to +150. Next, skeletal muscle index (SMI) is calculated by normalizing the measured skeletal muscle area for height in meters squared. Three major definitions of sarcopenia have been used in most previous papers on CT-determined sarcopenia (34). In 2008, Prado *et al.* firstly reported a CT-determined definition of sarcopenia: SMI <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women (Prado's definition) (35). In 2011, the International definition was proposed by a panel of international experts: SMI <55 cm^2/m^2 for men and <39 cm^2/m^2 for women (36). In 2013, Martin *et al.* proposed a body mass index (BMI)-incorporated definition of sarcopenia: SMI <43 cm^2/m^2 for males with BMI <25 kg/m^2, <53 cm^2/m^2 for males with BMI ≥25 kg/m^2, and <41 cm^2/m^2

Table 1 The search strategy summary

Items	Specification
Date of search	Apr. 21st, 2022
Databases and other sources searched	PubMed and Scopus
Search terms used	Search terms used were as follows: 'muscle-invasive bladder cancer' and 'bladder preservation therapy' and 'sarcopenia'; 'muscle-invasive bladder cancer' and 'trimodal therapy' and 'sarcopenia'
Timeframe	No limits were placed
Inclusion and exclusion criteria	Review articles were excluded
Selection process	Literature search was conducted independently by HF and FK. Consensus was obtained by opening discussion

for females (Martin's definition) (11).

Moreover, only the psoas muscle area was quantified on axial CT scans at the lumbar vertebral level in many previous studies (37,38). Normalizing the psoas muscle area for height in meters squared yields the psoas muscle index (PMI). Several PMI-based definitions of sarcopenia have been proposed. Hamaguchi *et al.* defined sarcopenia as PMI <6.36 cm^2/m^2 for males and <3.92 cm^2/m^2 for females (37). Moreover, Japan Society of Hepatology proposed a definition of sarcopenia as follows: PMI <6.0 cm^2/m^2 for males and <3.4 cm^2/m^2 for females (38).

Methods

To investigate the effect of sarcopenia on oncological outcomes and complication rates of bladder preservation therapy in MIBC patients, the PubMed and Scopus databases were used to perform a literature review (*Table 1*). There were no restrictions on publication years. The following keywords were searched: 'muscle-invasive bladder cancer' and 'bladder preservation therapy' and 'sarcopenia'; 'muscle-invasive bladder cancer' and 'trimodal therapy' and 'sarcopenia'. Literature search was conducted independently by HF and FK. Consensus was obtained by opening discussion. Review articles were excluded. Finally, we included two studies that reported the impact of sarcopenia on responses to trimodal therapy and survival outcomes of bladder preservation therapy in MIBC patients and two studies that compared complication rates of bladder preservation therapy between MIBC patients with and without sarcopenia.

In this section, based on the result of our literature search, we review and discuss the oncological outcomes and perioperative complications of bladder preservation therapy in MIBC patients with sarcopenia.

Impact of sarcopenia on the oncological outcomes of bladder preservation therapy against MIBC

Two papers reported responses to trimodal therapy and survival outcomes of bladder preservation therapy in MIBC patients with or without sarcopenia (*Table 2*). Almarzouq *et al.* showed the oncological outcomes of trimodal therapy, including TURB, chemotherapy [cisplatin alone (weekly at a dose of 40 mg/m^2), or gemcitabine alone (weekly at a dose of 100 mg/m^2)], and radiotherapy (total dose: 44–66 Gy), using a cohort of 141 MIBC patients (39). They defined sarcopenia using the two definitions: the International and Martin's definitions. Sarcopenia was observed in 56.7% and 40.4% of the total patients using the International and Martin's definitions, respectively. Associations between sarcopenia and other clinicopathological parameters were evaluated using Student's T or Wilcoxon Rank test for continuous variables and Chi-Square or Fisher's exact test for categorical variables. In both definitions, sarcopenic patients were significantly older and had worse performance status compared with non-sarcopenic patients. Complete response (CR) rates to trimodal therapy in sarcopenic and non-sarcopenic patients were 72.5% and 75.4%, respectively, according to the International definition (P=0.51) and 75.4% and 72.6%, respectively, according to the Martin's definition (P=0.62). Moreover, sarcopenia by the International definition was significantly associated with overall survival (OS) in univariate analysis (P=0.035) but not in multivariate analysis (P=0.66) using the Cox proportional hazards model. Similar results were obtained for sarcopenia

Table 2 Oncological outcomes of bladder preservation therapy in MIBC patients with sarcopenia

Authors	No. of patients	No. of sarcopenic patients	Protocol and inclusion criteria	Response to trimodal therapy	Median follow-up	Survival outcomes	Reference
Almarzouq *et al*.	N=141	N=80 (56.7%) according to the International definition[†]; N=57 (40.4%) according to the Martin's definition[‡]	Trimodal therapy [TURB, chemotherapy (gemcitabine or cisplatin), and radiotherapy (44–66 Gy)]. No inclusion criteria	CR rates of sarcopenic and non-sarcopenic patients were 72.5% and 75.4%, respectively, in the International definition[†] (P=0.51) and 75.4% and 72.6%, respectively, in Martin's definition[‡] (P=0.62)	32 months	Sarcopenia by the International definition[†] was significantly associated with OS in univariate analysis (P=0.035) but not in multivariate analysis (P=0.66). Sarcopenia by Martin's definition[‡] was significantly associated with OS in univariate analysis (P=0.025) but not in multivariate analysis (P=0.19)	(39)
Tanaka *et al.*	N=126	N=68 (54.0%) according to the Martin's definition[‡]	Tetramodal therapy [TURB, chemotherapy (cisplatin), radiotherapy (40 Gy), and consolidative partial cystectomy with pelvic lymph node dissection]. Inclusion criteria was as follows: pathologically confirmed urothelial carcinoma; circumscription within ≤25% of the bladder surface; absence of bladder neck involvement; and absence of broad carcinoma *in situ*	CR rates of sarcopenic and non-sarcopenic patients were 85.3% and 81.0%, respectively (P=0.52)	48 months	In 90 patients who completed consolidative partial cystectomy, 5-year MIBC-RFS was both 97% (P=0.96) and 5-year CSS was both 94% (P=0.96) in sarcopenic and non-sarcopenic patients	(40)

[†], International definition: SMI <55 cm^2/m^2 for men and <39 cm^2/m^2 for women; [‡], Martin's definition: SMI <43 cm^2/m^2 for men with BMI <25 kg/m^2, <53 cm^2/m^2 for men with BMI ≥25 kg/m^2 and <41 cm^2/m^2 for women; , consolidative partial cystectomy was offered only to patients with a CR response, which was confirmed by urine cytology, magnetic resonance imaging and tumor site re-biopsy. MIBC, muscle-invasive bladder cancer; TURB, transurethral resection of the bladder tumor; CR, complete response; OS, overall survival; RFS, recurrence-free survival; CSS, cancer-specific survival; SMI, skeletal muscle index; BMI, body mass index.

Table 3 Complication rates of bladder preservation therapy in MIBC patients with sarcopenia/frailty

Authors	No. of patients	No. of sarcopenic patients	Protocol	Total complication rate	Major complication rate	Reference
Tanaka *et al.*	N=126	N=68 (54.0%) according to the Martin's definition‡	Tetramodal therapy [TURB, chemotherapy (cisplatin), radiotherapy (40 Gy), and consolidative partial cystectomy with pelvic lymph node dissection]	Total complication rates (Clavien-Dindo 1–5) in consolidative partial cystectomy were 22.4% and 46.3% in sarcopenic and non-sarcopenic patients, respectively (P=0.02)	Complication rates with Clavien-Dindo 3 in consolidative partial cystectomy were 4.1% and 12.2% in sarcopenic and non-sarcopenic patients, respectively (P=0.24). No Clavien-Dindo 4–5 complications were observed in either group	(40)
Fraisse *et al.*	N=29	N=13 (44.8%) according to the Martin's definition‡	Trimodal therapy [TURB, chemotherapy (cisplatin), and radiotherapy (20–80 Gy)]	Total complication rates (Clavien-Dindo 1–5) were 90.9% and 56.3% in sarcopenic and non-sarcopenic patients, respectively	Major complication rates (Clavien-Dindo 3–5) were 45.5% and 6.3% in sarcopenic and non-sarcopenic patients, respectively	(41)

‡, Martin's definition: SMI <43 cm^2/m^2 for men with BMI <25 kg/m^2, <53 cm^2/m^2 for men with BMI ≥25 kg/m^2 and <41 cm^2/m^2 for women. MIBC, muscle-invasive bladder cancer; TURB, transurethral resection of the bladder tumor; SMI, skeletal muscle index; BMI, body mass index.

by the Martin's definition; it was significantly associated with OS in univariate analysis (P=0.025) but not in multivariate analysis (P=0.19) using the Cox proportional hazards model. Tanaka *et al.* compared the oncological outcomes between sarcopenic and non-sarcopenic patients in 126 MIBC patients treated with tetramodal therapy, which includes TURB, chemotherapy [2 cycles of intravenous cisplatin (20 mg/body) for 5 days], radiotherapy (total dose: 40 Gy), and consolidative partial cystectomy with pelvic lymph node dissection (40). The inclusion criteria were as follows: pathologically confirmed urothelial carcinoma, circumscription within ≤25% of the bladder surface, the absence of the bladder neck involvement, and the absence of broad carcinoma *in situ*. In addition, consolidative partial cystectomy was performed only in patients with a clinical CR to trimodal therapy, which was confirmed by urine cytology, magnetic resonance imaging, and tumor site re-biopsy. A robotic-assisted laparoscopic approach was not used in consolidative partial cystectomy. Sarcopenia was diagnosed with 54.0% of the total patients using the Martin's definition. No significant associations were observed between sarcopenia and other clinicopathological parameters using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. CR rates to trimodal therapy were 85.3% and 81.0% in sarcopenic and non-sarcopenic patients, respectively (P=0.52). In 90 patients who completed consolidative partial cystectomy, survival outcomes were equivalent between 49 sarcopenic and 41 non-sarcopenic patients. Five-year MIBC-recurrence-free survival (RFS) was 97% (P=0.96) and 5-year CSS was 94% (P=0.96) in both sarcopenic and non-sarcopenic patients using the Kaplan-Meier method.

Impact of sarcopenia on perioperative complication rates of bladder preservation therapy against MIBC

Tanaka *et al.* reported complication rates in consolidative partial cystectomy using a cohort of MIBC patients treated with tetramodal therapy including TURB, chemotherapy, radiotherapy, and consolidative partial cystectomy with pelvic lymph node dissection (*Table 3*) (40). Total complication rates (Clavien-Dindo 1–5) are 22.4% and 46.3% in sarcopenic and non-sarcopenic patients, respectively (P=0.02). Moreover, the rates of Clavien-Dindo 3 complications that included bladder-anastomotic leaks, lymphoceles, and postoperative hemorrhage were 4.1% and 12.2% in sarcopenic and non-sarcopenic patients, respectively (P=0.24). There were no Clavien-Dindo 4–5 complications in either group. Fraisse *et al.* showed complication rates of trimodal therapy using 29 MIBC patients (*Table 3*) (41). The radiotherapy protocol consisted of two sequences of daily hypofractionated irradiations for

a total dose of 20 to 80 Gy. The dose per fraction ranged from 2 to 20 Gy. A tumor boost of 12 to 70 Gy and a lymph node boost of 44 Gy were performed in four and two patients, respectively. Sarcopenia was observed in 13 (44.8%) patients based on the Martin's definition. Total complication rates (Clavien-Dindo 1–5) were 90.9% and 56.3% in sarcopenic and non-sarcopenic patients, respectively. Major complication rates with Clavien-Dindo 3–5 were reported to be 45.5% and 6.3% in sarcopenic and non-sarcopenic patients, respectively.

Discussion

Previous studies reported that sarcopenia was significantly associated with worse prognosis and a higher complication rate in bladder cancer patients undergoing RC (20-23). This suggests that sarcopenic patients could be potentially unfit for RC. Meanwhile, two previous studies reported that sarcopenia did not affect the oncological outcomes of bladder preservation therapy against MIBC. Tanaka *et al.* showed equivalent CR rates to trimodal therapy between sarcopenic and non-sarcopenic patients (40) Moreover, in patients undergoing partial cystectomy after trimodal therapy, sarcopenia was not associated with lower 5-year MIBC-RFS or CSS. Because this study used the strict inclusion criteria to assure the oncological safety (pathologically confirmed urothelial carcinoma, circumscription within ≤25% of the bladder surface, the absence of bladder neck involvement, and the absence of broad carcinoma *in situ*), excellent survival outcomes might be yielded regardless of the presence of sarcopenia. In addition, because bladder preservation therapy is less invasive compared with RC, bladder preservation therapy might be more preferable rather than RC in MIBC patients with sarcopenia. Similarly, in the study reported by Almarzouq *et al.*, CR rates to trimodal therapy were comparable between sarcopenic and non-sarcopenic patients (39). Moreover, sarcopenia was not an independent predictor of OS. As inclusion criteria for bladder preservation therapy were not specified in their study, these results would be insufficient to evaluate whether bladder preservation therapy can be a standard of care for sarcopenic patients or not.

Tanaka *et al.* reported that complication rates of consolidative partial cystectomy are comparable between sarcopenic and non-sarcopenic patients (40). This result would be attributed to less invasiveness of partial cystectomy compared with RC. Only Fraisse *et al.* reported complication rates of trimodal therapy in MIBC patients with sarcopenia (41). Sarcopenic patients showed higher rates of total and severe complications compared with non-sarcopenic patients. However, their cohort included only 29 patients and thus it is mandatory to validate their results in a larger cohort of trimodal therapy.

Recently, the advent of ICIs has shifted the paradigm of bladder cancer treatment (42). Currently, there are several ongoing clinical trials of bladder preservation therapy that combines TURB, chemoradiotherapy, and ICIs (43,44). ICIs can enhance abscopal effects by augmenting anti-cancer immunity in combination with radiotherapy or chemoradiotherapy (45,46). Thus, the use of ICIs may expand the indication of bladder preservation therapy including MIBC patients with metastatic lesions. This suggests that more sarcopenic patients with cancer cachexia might seek bladder preservation therapy. Given that chemotherapy is toxic in sarcopenic patients (19), other immunogenic therapy such as near-infrared photoimmunotherapy rather than chemoradiotherapy may be suitable for sarcopenic patients in combination with ICIs (47,48). Because sarcopenia was associated with poorer therapeutic efficacy of ICIs (24), further evaluation is necessary to determine the significance of sarcopenia in the management of bladder preservation therapy in the ICI era.

This study has several limitations. First, this study included only three articles and thus the sample size was limited. Second, all the included studies used a single method of measuring skeletal muscle mass. Still, multiple definitions of sarcopenia based on SMI was analyzed, Third, detailed data about patient characteristics and complications were not reported in all the included studies. Finally, all the included studies had limited follow-up period that may impact oncological outcomes.

In conclusion, sarcopenia appears not to affect responses to trimodal therapy and prognosis in MIBC patients treated with bladder preservation therapy. Because of limited evidence, it is unclear whether sarcopenia increases complication rates of bladder preservation therapy or not. Still, given its less invasiveness compared with RC, bladder preservation therapy could be a viable alternative in carefully selected MIBC patients regardless of the presence of sarcopenia. Further studies are necessary to elucidate whether bladder preservation therapy can be a standard treatment in MIBC patients with sarcopenia.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-355/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-355/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-355/coif). HF serves as an unpaid editorial board member of *Translational Andrology and Urology* from May 2022 to April 2024. FK has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol 2021;79:82-104.
3. Gilbert SM, Wood DP, Dunn RL, et al. Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI). Cancer 2007;109:1756-62.
4. Novara G, Catto JW, Wilson T, et al. Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. Eur Urol 2015;67:376-401.
5. Kessler ER, Kukreja JB, Geiger CL, et al. Treating Elderly Patients With Muscle-Invasive Bladder Cancer. J Natl Compr Canc Netw 2020;18:783-90.
6. Fukushima H, Koga F. Impact of sarcopenia in the management of urological cancer patients. Expert Rev Anticancer Ther 2017;17:455-66.
7. Fukushima H, Takemura K, Suzuki H, et al. Impact of Sarcopenia as a Prognostic Biomarker of Bladder Cancer. Int J Mol Sci 2018;19:2999.
8. Fukushima H, Fujii Y, Koga F. Metabolic and Molecular Basis of Sarcopenia: Implications in the Management of Urothelial Carcinoma. Int J Mol Sci 2019;20:760.
9. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755-63.
10. Dhillon RJ, Hasni S. Pathogenesis and Management of Sarcopenia. Clin Geriatr Med 2017;33:17-26.
11. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013;31:1539-47.
12. Harada K, Ida S, Baba Y, et al. Prognostic and clinical impact of sarcopenia in esophageal squamous cell carcinoma. Dis Esophagus 2016;29:627-33.
13. Lee JS, Kim YS, Kim EY, et al. Prognostic significance of CT-determined sarcopenia in patients with advanced gastric cancer. PLoS One 2018;13:e0202700.
14. Nagpal P, Pruthi DS, Pandey M, et al. Impact of sarcopenia in locally advanced head and neck cancer treated with chemoradiation: An Indian tertiary care hospital experience. Oral Oncol 2021;121:105483.
15. Fukushima H, Nakanishi Y, Kataoka M, et al. Prognostic significance of sarcopenia in upper tract urothelial carcinoma patients treated with radical nephroureterectomy. Cancer Med 2016;5:2213-20.
16. Lee JH, Jee BA, Kim JH, et al. Prognostic Impact of Sarcopenia in Patients with Metastatic Hormone-Sensitive Prostate Cancer. Cancers (Basel) 2021;13:6345.
17. Psutka SP, Boorjian SA, Moynagh MR, et al. Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer. J Urol 2016;195:270-6.
18. Wahlen BM, Mekkodathil A, Al-Thani H, et al. Impact

of sarcopenia in trauma and surgical patient population: A literature review. Asian J Surg 2020;43:647-53.
19. Tan BH, Brammer K, Randhawa N, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. Eur J Surg Oncol 2015;41:333-8.
20. Mayr R, Fritsche HM, Zeman F, et al. Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. World J Urol 2018;36:1201-7.
21. Psutka SP, Carrasco A, Schmit GD, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. Cancer 2014;120:2910-8.
22. Smith AB, Deal AM, Yu H, et al. Sarcopenia as a predictor of complications and survival following radical cystectomy. J Urol 2014;191:1714-20.
23. Mayr R, Gierth M, Zeman F, et al. Sarcopenia as a comorbidity-independent predictor of survival following radical cystectomy for bladder cancer. J Cachexia Sarcopenia Muscle 2018;9:505-13.
24. Fukushima H, Fukuda S, Moriyama S, et al. Impact of sarcopenia on the efficacy of pembrolizumab in patients with advanced urothelial carcinoma: a preliminary report. Anticancer Drugs 2020;31:866-71.
25. Koga F, Takemura K, Fukushima H. Biomarkers for Predicting Clinical Outcomes of Chemoradiation-Based Bladder Preservation Therapy for Muscle-Invasive Bladder Cancer. Int J Mol Sci 2018;19:2777.
26. Koga F, Kihara K. Selective bladder preservation with curative intent for muscle-invasive bladder cancer: a contemporary review. Int J Urol 2012;19:388-401.
27. Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002;20:3061-71.
28. Koga F, Yoshida S, Kawakami S, et al. Low-dose chemoradiotherapy followed by partial or radical cystectomy against muscle-invasive bladder cancer: an intent-to-treat survival analysis. Urology 2008;72:384-8.
29. Zietman AL, Sacco D, Skowronski U, et al. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. J Urol 2003;170:1772-6.
30. Kijima T, Tanaka H, Koga F, et al. Selective tetramodal bladder-preservation therapy, incorporating induction chemoradiotherapy and consolidative partial cystectomy with pelvic lymph node dissection for muscle-invasive bladder cancer: oncological and functional outcomes of 107 patients. BJU Int 2019;124:242-50.
31. Faron A, Sprinkart AM, Kuetting DLR, et al. Body composition analysis using CT and MRI: intra-individual intermodal comparison of muscle mass and myosteatosis. Sci Rep 2020;10:11765.
32. Fukushima H, Kataoka M, Nakanishi Y, et al. Posttherapeutic skeletal muscle mass recovery predicts favorable prognosis in patients with advanced urothelial carcinoma receiving first-line platinum-based chemotherapy. Urol Oncol 2018;36:156.e9-156.e16.
33. Fukushima H, Nakanishi Y, Kataoka M, et al. Postoperative Changes in Skeletal Muscle Mass Predict Survival of Patients With Metastatic Renal Cell Carcinoma Undergoing Cytoreductive Nephrectomy. Clin Genitourin Cancer 2017;15:e229-38.
34. Taguchi S, Nakagawa T, Uemura Y, et al. Comparison of major definitions of sarcopenia based on the skeletal muscle index in patients with urothelial carcinoma. Future Oncol 2021;17:197-203.
35. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629-35.
36. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489-95.
37. Hamaguchi Y, Kaido T, Okumura S, et al. Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults. Nutrition 2016;32:1200-5.
38. Nishikawa H, Shiraki M, Hiramatsu A, et al. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res 2016;46:951-63.
39. Almarzouq A, Kool R, Al Bulushi Y, et al. Impact of sarcopenia on outcomes of patients treated with trimodal therapy for muscle invasive bladder cancer. Urol Oncol 2022;40:194.e15-22.
40. Tanaka H, Fukushima H, Kijima T, et al. Feasibility and outcomes of selective tetramodal bladder-preservation therapy in elderly patients with muscle-invasive bladder cancer. Int J Urol 2020;27:236-43.
41. Fraisse G, Renard Y, Lebacle C, et al. Is sarcopenia a morbi-mortality factor in the treatment of localized

muscle-invasive bladder cancer? Prog Urol 2020;30:41-50.
42. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.
43. Marcq G, Souhami L, Cury FL, et al. Phase 1 Trial of Atezolizumab Plus Trimodal Therapy in Patients With Localized Muscle-Invasive Bladder Cancer. Int J Radiat Oncol Biol Phys 2021;110:738-41.
44. van Hattum JW, de Ruiter BM, Oddens JR, et al. Bladder-Sparing Chemoradiotherapy Combined with Immune Checkpoint Inhibition for Locally Advanced Urothelial Bladder Cancer-A Review. Cancers (Basel) 2021;14:38.
45. Fukushima H, Yoshida S, Kijima T, et al. Combination of Cisplatin and Irradiation Induces Immunogenic Cell Death and Potentiates Postirradiation Anti-PD-1 Treatment Efficacy in Urothelial Carcinoma. Int J Mol Sci 2021;22:535.
46. Fukushima H, Kijima T, Fukuda S, et al. Impact of radiotherapy to the primary tumor on the efficacy of pembrolizumab for patients with advanced urothelial cancer: A preliminary study. Cancer Med 2020;9:8355-63.
47. Fukushima H, Turkbey B, Pinto PA, et al. Near-Infrared Photoimmunotherapy (NIR-PIT) in Urologic Cancers. Cancers (Basel) 2022;14:2996.
48. Fukushima H, Kato T, Furusawa A, et al. Intercellular adhesion molecule-1-targeted near-infrared photoimmunotherapy of triple-negative breast cancer. Cancer Sci 2022;113:3180-92.

Cite this article as: Fukushima H, Koga F. Impact of sarcopenia in bladder preservation therapy for muscle-invasive bladder cancer patients: a narrative review. Transl Androl Urol 2022;11(10):1433-1441. doi: 10.21037/tau-22-355

