Impact of Sarcopenia as a Prognostic Biomarker of Bladder Cancer

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Abstract

Sarcopenia, the degenerative and systemic loss of skeletal muscle mass, indicates patient frailty and impaired physical function. Sarcopenia can be caused by multiple factors, including advanced age, lack of exercise, poor nutritional status, inflammatory diseases, endocrine diseases, and malignancies. Recently, growing evidence has indicated the importance of sarcopenia in the management of patients with various cancers. Sarcopenia is associated with not only higher rates of treatment-related complications but also worse prognosis in cancer-bearing patients. In this article, we conducted a systematic literature review regarding the significance of sarcopenia as a prognostic biomarker of bladder cancer. We also reviewed recent studies focusing on the prognostic role of changes in skeletal muscle mass during the course of treatment in bladder cancer patients.

1. Introduction

Bladder cancer is the most common malignancy of the urinary tract in the United States, with approximately 81,000 new cases and 17,000 deaths each year.[1] The most major histology of bladder cancer is urothelial carcinoma. Based on the pathological depth of tumor invasion, bladder cancer is classified into two groups: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Whereas NMIBC is treated with bladder-preserving treatments, including transurethral resection of the bladder tumor and intravesical instillation therapy,[2] patients with MIBC generally require total cystectomy and urinary diversion as a curative treatment.[3] However, approximately half of MIBC patients undergoing total cystectomy die within five years because MIBC is potentially an aggressive disease and frequently progresses to a metastatic disease postoperatively.[4] Once MIBC patients develop distant metastasis, their prognoses are poor despite receiving systemic chemotherapy with a median overall survival (OS) of approximately 15 months.[5] Thus, bladder cancer is still a challenging disease, although the recent advent of immuno-oncology drugs is shifting the paradigm of the management of bladder cancer patients.[6] Pre-therapeutic risk assessment based on prognostic biomarkers can help clinicians to predict their outcomes and counsel patients about treatment options. Therefore, identifying prognostic biomarkers contributes to better

management for bladder cancer patients.

Sarcopenia is a syndrome representing the degenerative and systemic loss of skeletal muscle mass.[7] According to recent surveys, the prevalence of sarcopenia is relatively high, ranging from 15% at 65 years to 50% at 80 years.[8] Sarcopenia is associated with lower physical activity, morbidity, and mortality.[9, 10] Sarcopenic patients tend to have higher morbidity from infectious diseases,[11] metabolic syndrome,[12] insulin resistance,[13] and cardiovascular diseases.[14] Sarcopenia is pathophysiologically associated with various etiologies, including advanced age, lack of exercise, poor nutritional status, inflammatory diseases, and endocrine diseases.[7] Malignant diseases can also cause sarcopenia.[15] In patients with cancer cachexia, anorexia, poor nutrition, and systemic inflammation make the metabolic state more catabolic, resulting in sarcopenia.

Recent studies have shown the prognostic impact of sarcopenia in various cancers. Sarcopenic patients show significantly worse survival than non-sarcopenic counterparts with lung or gastrointestinal cancer [16, 17], hepatic cell carcinoma [18], esophageal cancer [19], lymphoma [20], melanoma [21], or renal cell carcinoma.[22, 23] In bladder cancer, the role of sarcopenia in predicting survival has been clarified. In this article, we conducted a systematic literature review on published studies to comprehensively summarize the current clinical evidence on the prognostic role of

sarcopenia in bladder cancer patients. We also reviewed recent studies focusing on

the prognostic importance of changes in skeletal muscle mass during the course of

treatment in bladder cancer patients.

2. Evaluation of sarcopenia using CT images

Sarcopenia can be evaluated by measuring skeletal muscle mass. Bioimpedance analysis, anthropometry, dual energy x-ray imaging, CT, and magnetic resonance imaging are recommended as methods to measure skeletal muscle mass by the European Working Group of Sarcopenia in Older People (EWGSOP).[7] In cancer-bearing patients, including bladder cancer patients, CT images are generally used in the evaluation of sarcopenia, since abdominal CT scans are routinely performed for diagnosis, staging, surveillance of recurrence after treatment, and assessment of therapeutic response.[24]

2.1. Measurement of skeletal muscle mass using CT images

Axial CT images at the lumbar vertebral level are used to measure skeletal muscle areas because the total lumbar-skeletal muscle cross-sectional area is linearly correlated to the whole-body skeletal muscle mass.[25] The total skeletal muscle area at the third lumbar vertebra, including 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 measured using software such as Slice-O-Matic (Tomovision, Montreal, Canada) and OsiriX imaging software (Pixmeo, Geneva, Switzerland). The cross-sectional

areas of skeletal muscle are identified using Hounsfield Unit thresholds of −29 to

+150.

2.2. Skeletal muscle index

Skeletal muscle index (SMI) is used the most widely in evaluating sarcopenia in

cancer-bearing patients. SMI is calculated by normalizing skeletal muscle area for

height in meters squared, as is body mass index (BMI). Two major established

definitions of sarcopenia have been proposed so far. First, the International

Consensus of Cancer Cachexia (ICCC) proposed cutoff values of SMI as 55 cm^2/m^2

for males and 39 cm^2/m^2 for females.[15] Second, Martin et al. defined BMI-

incorporated cutoff values of SMI as < 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 for females.[16] Both of

the two definitions were the best cutoffs to predict overall mortality using a cohort of

patients with lung or gastrointestinal cancer, and either of them was used to define

sarcopenia in most previous studies on bladder cancer.[24]

2.3. Psoas muscle index

In some previous studies, only the psoas muscle area was measured on axial CT

images at the lumbar vertebral level. The psoas muscle index (PMI) is calculated by

normalizing the psoas muscle area for height in meters squared. Although a

correlation between PMI and whole-body skeletal muscle mass has not yet been

evaluated, the strong correlation between PMI and SMI suggests that PMI also

represents whole-body skeletal muscle mass.[26] Hamaguchi et al. proposed the

cutoff values of PMI to define sarcopenia as 6.36 cm^2/m^2 for males and 3.92 cm^2/m^2

for females, using a cohort of adult donors for living donor liver transplantation.[26]

However, because their cohort included only Japanese patients, the use of their

values may be limited to Asian populations.

3. Hybrid nature of sarcopenia as a prognostic biomarker

Prognostic tumor biomarkers generally reflect tumor aggressiveness, including tumor stage, histological grade, lymphovascular invasion, and patient survival. Several prognostic biomarkers are related to the general condition of the host; e.g. age, sex, performance status, BMI, anemia, etc. Notably, sarcopenia reflects both tumor and host factors (Figure 1). Because sarcopenia develops as a consequence of tumor progression, tumor-induced systemic inflammation, or metabolic aberration, its presence indicates tumor aggressiveness. In addition, sarcopenic patients are characterized by poor general health and physical performance, which can contribute to worse prognosis of cancer-bearing patients. High prognostic performance of sarcopenia could be explained by its hybrid nature, which is a unique feature as a prognostic biomarker.

4. Systematic literature review

A systematic literature review was performed to search for studies investigating the prognostic role of sarcopenia in bladder cancer patients according to the PRISMA guidelines [27]. The search was restricted to articles written in English and performed using PubMed, Medline, and Cochrane Libraries by entering the terms "sarcopenia and urothelial carcinoma" and "sarcopenia and bladder cancer". Twenty-nine articles published from June 2014 to April 2018 were identified on April 1, 2018. Two independent investigators (H.F. and K.T.) conducted the literature search and selection of articles. Potential discrepancies were resolved by open discussion. Details of the search and article selection are summarized in the flow diagram (Figure 2). Studies were included if they were published as original articles investigating the prognostic role of sarcopenia in bladder cancer patients. Review articles, case reports, editorial comments, letters, meeting abstracts, and studies not meeting our inclusion criteria in their contents were excluded. Twelve articles were included in our systematic review, all of which were retrospective, and no study of level 1 evidence was included.

5. Prognostic role of sarcopenia in bladder cancer

Table 1 lists published studies on the prognostic role of sarcopenia in bladder cancer patients. Most studies reported that sarcopenia was associated with worse prognosis. A systematic literature review identified six studies involving patients undergoing radical cystectomy (due to high-risk NMIBC or MIBC) and four studies involving patients with inoperable locoregionally advanced and/or metastatic diseases. No studies investigated the association between sarcopenia and survival in low- or intermediate-risk NMIBC patients. Nine of the ten studies used either SMI or PMI to define sarcopenia.

5.1. Survival after radical cystectomy

Although radical cystectomy with pelvic lymph node dissection is the standard of care for high-risk NMIBC and MIBC patients, its main problems include high incidences of perioperative complications.[3] In the contemporary radical cystectomy series, the incidence of major complications of Clavien-Dindo classification grade 3 or greater ranges from 5 to 26%, with a mortality rate of 0-3.9%.[28] Several studies showed that sarcopenia is significantly associated with higher rates of perioperative complications of radical cystectomy.[29, 30]

As shown in Table 1, six studies reported the prognostic role of sarcopenia in

bladder cancer patients undergoing radical cystectomy.[30-35] Five of them revealed that sarcopenia is a significant predictor of cancer-specific survival (CSS) and OS.[31-35] Psutka et al. for the first time demonstrated that sarcopenia is an independent predictor for both poorer CSS and OS [31]. The 5-year CSS and OS rates were lower for sarcopenic patients than for non-sarcopenic counterparts (49% vs. 72% for CSS and 39% vs. 70% for OS, respectively). Three studies from Japan reported similar results to those of Psutka et al.[32-34] Recently, a multi-center retrospective study from Germany demonstrated that sarcopenia is an independent predictor for both poorer CSS and OS in 500 bladder cancer patients undergoing radical cystectomy.[35] Only one study, reported by Smith et al., showed no association between sarcopenia and OS.[30] This discrepant result may be due to the different methods for estimating skeletal muscle volume. Four studies calculated SMI, and three of them used the definition of sarcopenia proposed by Martin et al. However, Smith et al. calculated cross-sectional psoas muscle area using 3-dimensional computerized image analysis and defined sarcopenia using their own criteria.

Taken together, most previous studies demonstrated that sarcopenia is a significant poor prognostic factor in bladder cancer patients undergoing radical cystectomy.

5.2. Survival in inoperable advanced disease

Four studies evaluated the prognostic role of sarcopenia in patients with inoperable advanced bladder cancer (Table 1).[36-39] Because upper tract urothelial carcinoma is histologically and biologically similar to bladder cancer, three of them included advanced upper tract urothelial carcinoma in their cohorts.[36, 37, 39] Fukushima et al. showed for the first time that sarcopenia is an independent predictor for shorter OS in patients with advanced urothelial carcinoma (inoperable locoregionally advanced disease and/or metastatic diseases to lymph nodes or distant organs).[36] The median OS of sarcopenic patients was significantly shorter than that of non-sarcopenic counterparts (11 vs. 31 months). Taguchi et al. reported that sarcopenia is an independent predictor for shorter CSS in metastatic urothelial carcinoma patients receiving systemic chemotherapy as the first-line therapy.[37] Kasahara et al. showed the prognostic significance of sarcopenia in advanced bladder cancer patients receiving gemcitabine and nedaplatin therapy.[38] In addition, Abe et al. could not confirm the significance of sarcopenia in predicting OS, but they showed that SMI stratified by BMI was an independent predictor for shorter OS.[39]

Thus, previous studies indicated that sarcopenia is a significant poor prognostic factor in inoperable advanced bladder cancer patients.

6. Prognostic role of changes in skeletal muscle mass in bladder cancer

Because disease status and patient conditions can affect skeletal muscle mass in cancer-bearing patients, changes in skeletal muscle mass during and after treatments may represent post-therapeutic prognosis. As shown in Table 2, three studies investigated the prognostic role of changes in skeletal muscle mass during treatments in bladder cancer patients.[33, 40, 41] Miyake et al. reported that a 10% loss in psoas muscle volume before and after radical cystectomy was an independent predictor for shorter OS.[33] Fukushima et al. reported that post-therapeutic skeletal muscle mass recovery was an independent predictor for both better recurrence-free survival and OS in advanced urothelial carcinoma treated with platinum-based chemotherapy as the first-line therapy.[41] Meanwhile, Zargar et al. showed that decline in psoas muscle volume during neoadjuvant chemotherapy was not predictive of OS in bladder cancer patients treated with neoadjuvant chemotherapy and radical cystectomy.[40]

Although a paucity of data suggests the prognostic significance of changes in skeletal muscle mass during treatments among bladder cancer patients, further studies are needed to confirm this finding.

7. Therapeutic interventions for sarcopenia

Given the prognostic significance of sarcopenia and changes in skeletal muscle mass in bladder cancer patients, prevention of or recovery from sarcopenia may contribute to improving their prognosis. There are several studies to investigate nutritional support and exercise as therapeutic interventions for sarcopenia in cancer-bearing patients.

7.1. Nutritional support

Accumulating evidence shows the effect of nutritional support on sarcopenia. Because sarcopenia results from a decrease in protein synthesis and increase in protein degradation, protein supplementation can play a key role in nutritional support.[42] Moreover, n-3 fatty acids, including eicosapentaenoic acid and docosahexaenoic acid, can recover a cancer-induced hyper-catabolic state and improve sarcopenia and cachexia by its anti-inflammatory effects, involving the attenuation of NF-kB signaling, deceleration of the ubiquitin proteasome pathway, and antagonization of superoxide dismutase.[43-45] Moreover, n-3 fatty acids can mediate the induction of apoptosis and the reduced proliferation of tumor cells.[46] Recently, a randomized controlled study revealed that eicosapentaenoic acid improved postoperative survival in patients undergoing metastasectomy for liver

metastases from colorectal cancer.[47]

7.2. Exercise

Exercise, including aerobic exercise and resistance training, can contribute to the improvement of sarcopenia in cancer-bearing patients.[48, 49] Exercise can overcome sarcopenia by abrogating systemic inflammation and catabolism.[50] Exercise has been reported to contribute to maintaining skeletal muscle mass and function in breast cancer patients treated with systemic chemotherapy.[51] In addition, several studies demonstrated the anti-tumor effects of exercise. Exercise was shown to induce the secretion of interleukin-6 from muscles and elicit anti-tumor immunity in combination with epinephrine by redistributing natural killer cells to tumor microenvironments.[52] Exercise was shown to inhibit tumor growth by activating the Hippo tumor suppressor pathway via β-adrenergic signaling.[53]

8. Conclusions

In this review, we summarized reported series of the prognostic role of sarcopenia in bladder cancer patients. Sarcopenia is significantly associated with unfavorable prognosis in bladder cancer patients undergoing radical cystectomy. Moreover, sarcopenia is also a significant poor prognostic factor in patients with inoperable advanced bladder cancer. Thus, sarcopenia can be used as a prognostic biomarker in patients with bladder cancer at various stages. We reviewed reported series of the prognostic role of changes in skeletal muscle mass during treatments in bladder cancer patients. Recovery of skeletal muscle mass during treatments can be associated with improved prognosis of bladder cancer patients, whereas decline of skeletal muscle mass can reflect poor prognosis, indicating its role not only as a prognostic biomarker but also as a surrogate marker for treatment efficacy in bladder cancer patients. In addition, nutritional support and exercise may improve sarcopenia and have a favorable influence on the management of cancer-bearing patients. Future studies may clarify the prognostic value of these interventions in cancer-bearing patients.

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Author Contributions

All authors made substantial contributions to this work; acquisition and interpretation

of data by online search, H.F. and K.T.; draft and supervision of the work, H.F and F.K.;

revision of the work, H.F., K.T., H.S., and F.K. All authors have approved the final

version and agree to be personally accountable for the author's own contributions.

Conflicts of Interest

The authors declare no conflicts of interest.

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Figure Legends

Figure 1 Hybrid nature of sarcopenia.

Figure 2 Flow diagram of systematic literature search.

Table 1. Reported series of the prognostic role of sarcopenia in bladder cancer cancers

Study (year)	Country	No. of total patients	No. of sarcopenic patients	Cancer type	Therapeutic interventions	Definition of sarcopenia	Main findings	Ref.
Smith *et al.* (2014)	United States	200	77 (39%)	Bladder cancer	Radical cystectomy	TPA[†] < 653 cm^2/m^2 for males and < 523 cm^2/m^2 for females	The Kaplan-Meier curves showed no significant association between OS and sarcopenia (p = 0.36).	[30]
Psutka *et al.* (2014)	United States	205	141 (69%)	Bladder cancer	Radical cystectomy	SMI < 55 cm^2/m^2 for males and < 39 cm^2/m^2 for females	Sarcopenia was an independent poor prognostic factor with HR 2.14 for CSS (p = 0.007) and 1.93 for OS (p = 0.004).	[31]
Hirasawa *et al.* (2016)	Japan	136	65 (48%)	Bladder cancer	Radical cystectomy	SMI < 43 cm^2/m^2 for males with BMI < 25 cm^2/m^2, < 53 cm^2/m^2 for males with BMI ≥ 25 cm^2/m^2, and < 41 cm^2/m^2 for females	Sarcopenia was an independent poor prognostic factor with HR 2.3 for CSS (p = 0.015).	[32]
Miyake *et al.* (2017)	Japan	89	22 (25%)	Bladder cancer	Radical cystectomy	SMI < 43 cm^2/m^2 for males with BMI < 25 cm^2/m^2, < 53 cm^2/m^2 for males with BMI ≥ 25 cm^2/m^2, and < 41 cm^2/m^2 for females	Sarcopenia was an independent poor prognostic factor with HR 2.2 for OS (p = 0.03).	[33]

Study	Country	N	Sarcopenia n (%)	Cancer	Treatment	Definition	Findings	Ref
Saitoh-Maeda *et al.* (2018)	Japan	63 (male only)	141 (69%)	Bladder cancer	Radical cystectomy	PMI < 400 cm^2/m^2	In male patients, non-sarcopenic patients had a significantly better OS than sarcopenic counterparts (2,889 vs. 2,009 days; *p* = 0.023).	[34]
Mayr *et al.* (2018)	Germany	500	189 (38%)	Bladder cancer	Radical cystectomy	SMI < 43 cm^2/m^2 for males with BMI < 25 cm^2/m^2, < 53 cm^2/m^2 for males with BMI ≥ 25 cm^2/m^2, and < 41 cm^2/m^2 for females	Sarcopenia was an independent poor prognostic factor with HR 1.42 for CSS (p = 0.048) and 1.43 for OS (p = 0.01).	[35]
Fukushima *et al.* (2015)	Japan	88	67 (76%)	Advanced urothelial carcinoma	Miscellaneous	SMI < 43 cm^2/m^2 for males with BMI < 25 cm^2/m^2, < 53 cm^2/m^2 for males with BMI ≥ 25 cm^2/m^2, and < 41 cm^2/m^2 for females	Sarcopenia was an independent poor prognostic factor with HR 3.36 for OS (p < 0.001).	[36]
Taguchi *et al.* (2015)	Japan	100	Not reported	Metastatic urothelial carcinoma	Systemic chemotherapy	SMI < 55 cm^2/m^2 for males and < 39 cm^2/m^2 for females	Sarcopenia was an independent poor prognostic factor with HR 2.07 for CSS (p = 0.045).	[37]
Kasahara *et al.* (2017)	Japan	27	14 (52%)	Advanced bladder cancer	Systemic chemotherapy	PMI < 2.49 cm^2/m^2 for males and < 2.07 cm^2/m^2 for females	The OS of the non-sarcopenic group was significantly better than that of the sarcopenic group (561 vs. 223 days; *p* = 0.0150).	[38]

| Abe *et al.* (2018) | Japan | 87 | Not reported | Metastatic urothelial carcinoma | Systemic chemotherapy | SMI < 55 cm^2/m^2 for males and < 39 cm^2/m^2 for females | Sarcopenia was not significantly associated with OS (p = 0.11). SMI stratified by BMI was an independent predictor for shorter OS (p = 0.026). | [39] |

Abbreviations: BMI = body mass index; CSS = cancer-specific survival; HR = hazard ratio; OS = overall survival; PMI = psoas muscle index; SMI = skeletal muscle index; TPA = total psoas area.

†TPA was calculated by measuring the cross-sectional area of the right and left psoas muscles on CT using 3-dimensional computerized image analysis.