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Original Article

Sarcopenia is a poor prognostic factor of castration-resistant prostate cancer treated with docetaxel therapy

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ABSTRACT

Background: Sarcopenia is a geriatric syndrome that is characterized by the gradual muscle loss and frailty in the elderly. Meanwhile, the prevalence of prostate cancer is on the rise worldwide. Mainstay treatments for metastatic prostate cancer are androgen-deprivation therapy and taxane-based chemotherapy. Owing to the indolent nature of prostate cancer, these treatments tend to be long-lasting, giving rise to the problem of tolerance to the treatments. Especially given the fact that long-term chemotherapy is closely associated with muscle loss, we aimed to elucidate the correlation between chemotherapy and sarcopenia in the clinical setting.

Materials and methods: This study was a retrospective study. Participants with castration-resistant prostate cancer were recruited from November 2009 to September 2015.

Participants were recruited at two hospitals, Juntendo and Teikyo University Hospital, Tokyo, Japan.

Participants were 77 Japanese males with castration-resistant prostate cancer who underwent docetaxel chemotherapy.

Sarcopenia was defined as L3-psoas muscle index < 5.7 cm^2/m^2. We statistically investigated whether the existence of sarcopenia has an impact on the survival time, and identified potential covariates that affect it.

Results: Out of 77 patients, 26 patients (34%) were diagnosed as sarcopenia. Analysis showed that sarcopenia is independently associated with mortality risk (hazards ratio = 2.74, $P = 0.0055$). Sarcopenic patients showed significant decrease in body mass index, pretreatment hemoglobin, C-related protein, and L3-psoas muscle index as compared with nonsarcopenic patients. The median observation period was 499 days (330–790). Thirty-five patients (45%) died of prostate cancer during that period. Sarcopenic patients showed significantly shorter survival time after the initiation of docetaxel treatments ($P = 0.0055$).

Conclusion: Sarcopenia is an independent predictive factor for a poor tolerance to docetaxel treatment. Given that cessation of the treatment leads to death from the disease, our study identified sarcopenia as an independent factor that raises mortality risk.

Introduction

Most cancers afflict aged patients, including prostate cancers. In the aged patients, physical ability and cognitive function tend to deteriorate with increasing age. Recently, these common health conditions seen in the aged individuals are collectively termed as geriatric syndrome. Elderly patients with cancer experience a higher prevalence of geriatric syndromes than those without cancer.[1] Among geriatric syndromes, sarcopenia is one of the most important symptoms. In patients with various disease as well as cancer, frailty and sarcopenia prevalence is high, and both syndromes are predictors of being hospitalized and activities of daily life (ADL) disability.[2]

Sarcopenia is defined as progressive loss of skeletal muscle and muscle strength.[3,4] The previous study showed that the prevalence rate of sarcopenia in a representative sample of older Japanese

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adults was 8.2% based on the European Working Group on Sarcopenia in Older People algorithm.[5] Moreover, in elderly patients, excessive catabolism and appetite loss caused by cancers further exacerbate co-existing sarcopenia, imposing detrimental effects on posttreatment ADL, treatment-related complications, and overall treatment outcomes. Thus, sarcopenia is broadly categorized into primary and secondary sarcopenia depending on its cause; primary sarcopenia is considered to be age-related, on the other hand, secondary sarcopenia is triggered by other causes such as malnutrition and disuse syndrome.

To date, androgen-deprivation therapy (ADT) by chemical or surgical castration has been mainstay treatments for prostate cancer. Although ADT is the first treatment option for metastatic prostate cancer, most cases eventually progress to castration-resistant prostate cancer (CRPC) that is characterized by prostate-specific antigen (PSA) elevation and progression of primary and metastatic lesion. In a large international multicenter stage III trial (TAX327), docetaxel with prednisone were compared with a combination of mitoxantrone and prednisone for CRPC patients. The median overall survival was 19.6 months in the 3-weekly docetaxel arm and 16.7 months after mitoxantrone ($P = 0.003$).[6,7] The conclusion was that 3-weekly docetaxel was superior to mitoxantrone in prolongation of survival. However, the side-effects of docetaxel chemotherapy included grade III to IV neutropenia in 32% of patients treated with 3-weekly docetaxel, and other side-effects included fatigue, alopecia, diarrhea, neuropathy, and male dystrophy. Moreover, similar trends in survival between treatment arms were seen for patients greater than and less than the median age of 68 years (median overall survival: 18.1 vs. 17.6 months, respectively).[7] Thus docetaxel could be equivalently effective for elderly CRPC patients as well as younger ones. However, evidences have been insufficient yet for validating of the association between effectiveness of docetaxel and patients' muscle status.

Herein, we assessed muscle mass of CRPC patients and investigated the impact of sarcopenia on the survival time and treatment outcomes of docetaxel. We also evaluated which covariates significantly affect the outcome.

Methods

Participants

We retrospectively analyzed 77 Japanese patients with CRPC who underwent docetaxel chemotherapy at Juntendo and Teikyo University Hospital (Tokyo, Japan) from November 2009 to September 2015. The definition of CRPC is based on the Prostate Cancer Clinical Trials Working Group 3.[8]

Measures

We retrospectively reviewed medical records of 77 Japanese patients. For a diagnosis of sarcopenia, cross-sectional area of L3-psoas muscle was determined by computed tomography (CT) scan, and L3-psoas muscle index (PMI) was calculated by dividing that value by the square of height in meters. Sarcopenia was defined as PMI < 5.7 cm^2/m^2. For graphical analysis of CT scan, FUJIFILM synapse (FUJIFILM, Tokyo, Japan) and DICOM Viewer (GE healthcare, Chicago, IL) were employed. The area of L3-psoas muscle was measured by using region of interest tool for subsequent calculation of PMI. We set the cut-off value at PMI < 5.7 cm^2/m^2 for a diagnosis of sarcopenia in accordance with the previous reports.[9–12]

Graphical analysis was done by one specific investigator (A.O.) to minimize technical deviation. Fig. 1 shows the actual representative graphical comparison of sarcopenic and non-sarcopenic patients at the L3 level.

Statistical analysis

Patients were classified into two groups: sarcopenic or non-sarcopenic in accordance with the above criteria. The following clinically important covariates were compared between two groups: treatment-starting age, body mass index (BMI), PSA value at first clinic visit, Gleason score, risk stratification, history of radical treatment, the metastases to bone/lymph node/visceral organs, other blood examinations [pretreatment PSA value, hemoglobin (Hb), serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum albumin, C-reactive protein (CRP), neutrophil–lymphocyte ratio (NLR), and Charlson Comorbidity Index (CCI). For continuous variables, the median value and interquartile ranges were used, and they were assessed by Wilcoxon signed-rank test. For categorical variables, frequency and percentage were used, and they were compared by Chi-square test and Cochran's test. Clinical staging and the timing of the intervention were determined by attending doctors. The Kaplan–Meier method was used to draw the survival curve, and log-rank test was used to compare the survival rate of two groups. Univariate and multivariate Cox proportional-hazards survival analyses were used to identify factors associated with death from prostate cancer (indicated as 95% confidence intervals). In multivariate analysis, we set the number of independent variables in accordance with the concept of events per variables.[13] Backward selection was used to choose independent variables for multivariate analysis.

Statistical software, JMP11 (SAS Institute, Cary, NC), was used for the statistical analyses. Statistical significance was defined as $P < 0.05$.

Results

In our study, the median value of PMI was 6.2 cm^2/m^2 (5.03–7.55), and 26 cases (34%) were diagnosed as sarcopenia. The background factors were compared between two groups. As a result, BMI ($P = 0.0074$), Hb ($P = 0.0112$), and CRP ($P = 0.0287$) were significantly lower in the sarcopenic group. By contrast, clinical stage, general condition, and the existence of comorbidity were not significantly different between two groups.

Clinical background of patients is indicated in Table 1. The median age was 70 years (65–76), the median BMI value was 23.98 kg/m^2 (21.29–25.93), the median initial PSA value was 84.0 ng/ml (25.0–307.5), and Gleason score was greater than 7 in 71 cases (85%). The median time period until progression to castration-resistant state was 838 days (441–1618). Most cases were categorized as a high-risk group at the time of diagnosis, and 57 cases (68%) had metastases. The general condition before the administration of docetaxel was evaluated by performance status and CCI. Performance status was less than 1 in all cases, and CCI was less than 2 in 71 cases (92%). The median observational period 499 days (330–790), during which 35 patients (45%) died.

Survival time after docetaxel administration was significantly shorter in the sarcopenic group (Fig. 2, Log-rank test, $P = 0.0027$). Cessation of docetaxel treatment was because of the progression of the disease in 39 cases (47%), which was not significantly different between two groups. In univariate Cox proportional-hazards model, sarcopenia, albumin, NLR, LDH, Hb, ALP were significantly associated with patients' death. For multivariate Cox proportional-hazards model to predict patients' death, we determined the number of variables using the concept of events per variables.[12] In events per variables, using one independent variable for 10 events is considered appropriate. Since there were 34 deaths in our study,

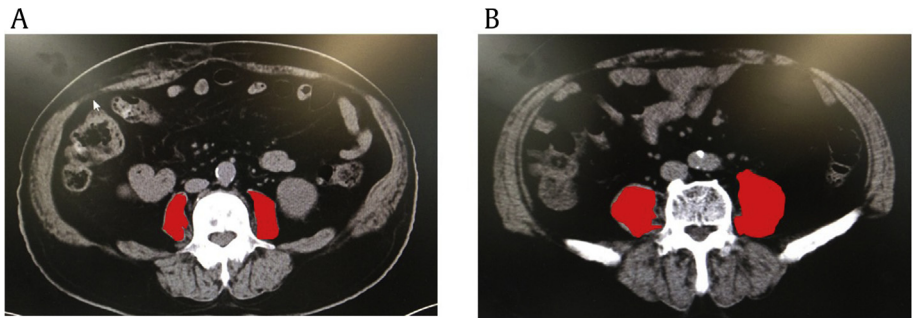
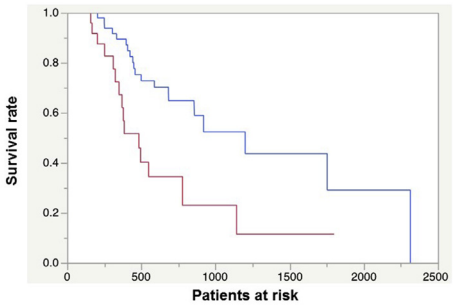


Fig. 1. The actual representative graphical comparison of the sarcopenic and nonsarcopenic patients at the L3 level. The representation of sarcopenic group (A) and nonsarcopenic group (B).

Table 1
Comparison of clinicopathological features between patients with and without sarcopenia.

Factors	Total N = 77	Nonsarcopenia group N = 51	Sarcopenia group N = 26	*P*
Median age at docetaxel (range)	70 (65–76)	69 (64–76)	73 (68.8–79.5)	0.0346
Median BMI (kg/m^2) (range)	23.98 (21.29–25.93)	24.27 (24.27–26.46)	22.45 (19.58–24.91)	0.0074
Median PSA at first visit (ng/ml) (range)	83.95 (25.02–307.5)	83.85 (23.25–214.2)	91.18 (26.55–566.75)	0.6014
Gleason score (No)				0.3563
<8	6	5 (9.80%)	1 (3.85%)	
8≦	71	46 (90.20%)	25 (96.15%)	
D'amico classification at first visit (No)				0.5925
Low	1	1 (1.96%)	0	
Intermediate	1	1 (1.96%)	0	
High	75	49 (96.08%)	26 (100%)	
Total prostatectomy (No)				0.5009
Yes	5	4 (7.84%)	1 (3.85%)	
No	72	47 (92.16%)	25 (96.15%)	
Local radiation therapy (No)				0.3524
Yes	23	17 (33.33%)	6 (23.08%)	
No	54	34 (66.67%)	20 (76.92%)	
Bone metastasis at docetaxel start (No)				0.8192
Yes	55	36 (70.59%)	19 (73.08%)	
No	22	15 (29.41%)	7 (26.92%)	
Lymph node metastasis at docetaxel start (No)				0.0912
Yes	34	26 (50.98%)	8 (30.77%)	
No	43	25 (49.02%)	18 (69.23%)	
Visceral organ metastasis at docetaxel start (No)				0.9725
Yes	12	8 (15.69%)	4 (15.38%)	
No	65	43 (84.31%)	22 (84.62%)	
PSA at docetaxel start (ng/ml) (range)		38.59 (10.46–172)	24.72 (8.19–76.92)	0.279
Median Hb at docetaxel start (g/dl) (range)	12.1 (11.05–13.35)	12.1 (11.3–13.5)	11.3 (10.3–12.4)	0.0112
Median ALP at docetaxel start (IU/l) (range)	254 (180–422)	261 (181–454)	254 (176–460)	1
Median LDH at docetaxel start (IU/l) (range)	211 (169–262)	222 (185–253)	182 (158–286)	0.1585
Median Alb at docetaxel start (mg/dl) (range)	4.1 (3.8–4.2)	4.1 (3.8–4.3)	4.1 (3.6–4.2)	0.7895
Median CRP at docetaxel start (mg/dl) (range)	0.3 (0.1–1.1)	0.2 (0.1–0.7)	0.75 (0.12–2.33)	0.0287
Median ratio of the number of neutrophils and lymphocytes (range)	3.05 (2.25–5.54)	2.98 (2.08–5.50)	3.66 (2.52–5.99)	0.2158
Median PMI at docetaxel start (cm^2/m^2)	6.28 (5.03–7.55)	7.14 (6.28–8.11)	4.58 (3.84–5.07)	<0.0001
Median time to CRPC (duration of primary ADT) (day) (range)	838 (441–1618)	1085 (446–1697)	758 (429–1246)	0.3771
Charlson comorbidity index (No)				0.3812
≦2	71	48 (94.12%)	23 (88.46%)	
3≦	6	3 (5.88%)	3 (11.54%)	
Median docetaxel total dose (mg/m^2) (range)	770 (429.7–1225)	840 (460–1385)	559.5 (395–1005)	0.1817
PSA nadir after docetaxel start (ng/ml) (range)	8.02 (1.62–36.0)	8.019 (1.275–23.514)	7.75 (2.33–80.66)	0.5181
Reason for docetaxel discontinued (No)				0.4633
Progression	49	31 (60.78%)	18 (69.23%)	
Side-effect	28	20 (39.22%)	8 (30.77%)	
Death by cancer (No)				0.1753
Yes	34	19 (37.25%)	15 (57.69%)	
No	38	29 (56.86%)	9 (34.62%)	
Unknown	5	3 (5.88%)	2 (7.69%)	

ADT, androgen-deprivation therapy; ALP, serum alkaline phosphatase; BMI, body mass index; CRP, C-reactive protein; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; LDH, lactate dehydrogenase; PMI, L3-psoas muscle index; PSA, prostate-specific antigen.



Survival Time (days)	0	500	1000	1500	2000
sarcopenia	24	8	2	1	0
Survival Rate		0.5228	0.27332	0.14289	0.0747
nonsarcopenia	49	31	9	5	1
Survival Rate		0.75547	0.57073	0.43117	0.32573

Fig. 2. Survival time after docetaxel administration was significantly shorter in the sarcopenic group (red line) than the nonsarcopenia (blue line). (Log-rank test $P = 0.0027$).

we decided to use three independent variables for multivariate analysis. Using backward selection, we narrowed down aforementioned six independent variables (sarcopenia, albumin, NLR, LDH, Hb, and ALP) to sarcopenia, NLR and LDH.

Proportional hazard model indicated that sarcopenia together with NLR and LDH is an independent factor that attributes to increased mortality risk (Table 2).

Discussion

In the current study, more than 30% of patients were diagnosed as sarcopenia, which is higher than the reported average prevalence, which was approximately 5–13% in 60~70-year-old patients in the United States and Europe.[14] This can be ascribable to several factors such as excessive catabolism caused by cancers and malnutrition as a result of appetite loss, in addition to aging. Several earlier studies pointed out that ADT causes body weight loss and muscle loss of lower limbs, leading to sarcopenia.[15,16] Given these results, we assumed that ADT was the major reason for this higher prevalence of sarcopenia in our study. However, contrary to our expectations, the median time to develop CRPC (the duration of primary ADT) was not significantly different between sarcopenic and nonsarcopenic groups in our study. Instead, our results suggested that several distinct lifestyle-related factors intricately contributed to this tendency.

The novel finding of our study is that the existence of sarcopenia itself independently shortens survival time and raises the mortality rate. This result means that by assessing the degree of sarcopenia of each patient, we can provide tailor-made medicine such that unnecessary anticancer treatment can be avoided for unfit patients. Furthermore, our result lends credibility to the clinical notion that novel antiandrogen agents with generally milder side-effects should be given for sarcopenic CRPC patients instead of cytotoxic taxane-based chemotherapy.

With regard to factors associated with a prognosis of CRPC treated with taxane-based chemotherapy, the earlier studies have demonstrated that factors such as bone metastases measured by bone scan index, serum CRP, and NLR are associated with a poor prognosis.[17–19] In our study, sarcopenia itself can be a predictive factor for an increased mortality rate. The earlier studies already suggested that sarcopenia raises the mortality rate in renal, pancreatic, hepatic, esophageal, and mammary carcinoma.[20–26] Most patients suffering from cancer cachexia have sarcopenia, providing a convincing rationale that aggressive chemotherapy should not be selected for these patients. It is suggested that preceding studies regarding sarcopenia include patients with preexisting cancer cachexia, which might have been responsible for increased mortality rate.

For a diagnosis of sarcopenia, we employed cross-sectional area of L3-psoas muscle determined by CT scan. Area of L3-psoas muscle is considered to be an accurate reflection of a total muscle mass of the whole body and utilized for analyses of several other cancer types. However, the international threshold of PMI for a diagnosis of sarcopenia is yet to be defined; thus, the cut-off value varies among each study (e.g., PMI < 5.896 cm^2/m^2 for pancreatic cancer, PMI < 6.15 cm^2/m^2 for extrahepatic bile duct cancer),[27,28] making its interpretation difficult. Furthermore, as another limitation in evaluating PMI, area of L3-psoas muscle is determined by manual tracing, which can cause biases and technical deviation depending on skills of assessors. To the best of our knowledge, the standardized methodology is yet to be reported. To overcome these limitations, dual-energy X-ray absorptiometry (DEXA) has been developed, which enabled the accurate measurement of bone mineral density, body fat, and body mass subtracted by body fat. In DEXA, two types of X-ray beams with different energy level are emitted, followed by the evaluation of difference in absorption of the photons. DEXA has been reported to reflect somatic muscle

Table 2
Univariate and multivariate cox proportional hazards analysis of variables associated with patients' risk of death from CRPC after docetaxel treatment.

Factors	Univariate analysis	*P*	Multivariate analysis	*P*
	HR (95% CI)		HR (95% CI)	
Sarcopenia (reference: No)	2.74 (1.36–5.44)	0.0055	2.84 (1.22–6.69)	0.016
Age at docetaxel >75 (age)	1.59 (0.78–3.17)	0.196		
BMI < 24 (kg/m^2)	1.45 (0.73–2.98)	0.2925		
PSA at first visit >100 (ng/ml)	0.67 (0.32–1.36)	0.2736		
Total prostatectomy	0.65 (0.27–1.39)	0.2823		
PSA at docetaxel start >20 (ng/ml)	1.59 (0.79–3.29)	0.1903		
Serum albumin at docetaxel start <3.5 (mg/dl)	2.81 (1.01–6.74)	0.0472		
Lymph node positive at docetaxel start (reference: negative)	1.19 (0.60–2.51)	0.613		
Bone metastasis at docetaxel start	1.43 (0.68–3.29)	0.359		
Visceral organ metastasis at docetaxel start	1.08 (0.37–2.57)	0.8776		
Duration of primary ADT treatment >900 (days)	0.72 (0.36–1.42)	0.3452		
The ratio of the number of neutrophils and lymphocytes 4≦	4.15 (1.78–10.80)	0.0009	5.74 (2.23–16.40)	0.0002
LDH at docetaxel start >250 (IU/l)	2.14 (1.01–4.36)	0.0479	4.00 (1.58–10.08)	0.0041
Hb at docetaxel star <12.1 (g/dl)	2.09 (1.05–4.29)	0.0348		
ALP at docetaxel start >400 (IU/l)	2.43 (1.14–5.08)	0.0216		

ADT, androgen-deprivation therapy; ALP, serum alkaline phosphatase; BMI, body mass index; CI, confidence interval; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; HR, hazards ratio; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

mass more accurately.[29,30] Additional advantages of DEXA can be enumerated as follows: reduced irradiation and less unwanted artifact caused by water mass. As a further support for reliability of DEXA, the European Working Group on Sarcopenia in Older People and Asian Working Group for Sarcopenia have adopted DEXA to make a diagnosis. Recently, the Foundation for the National Institutes of Health Sarcopenia Project reported usefulness of DEXA measures combined with BMI and appendicular lean mass,[31] thus the classification based on combination of these various indicators allows for more reliable and standardized diagnosis.

To date, it has been recognized that various metabolic complications, such as anemia, osteoporosis, muscle loss, and fat gain, can occur as adverse effects of ADT.[15,32] Therefore, it is plausible that CRPC patients are more susceptible to sarcopenia, especially given that prostate cancer mostly afflicts the elderly. In contrast to this hypothesis, we could not confirm a significant correlation between the duration of ADT and muscle loss. However, it requires a further large-scale prospective study so as to elucidate the relationship between ADT and muscle loss. Moreover, detrimental effect of sarcopenia on survival rate is mostly ascribable to deteriorated ADL. Thus, as a future assignment, we need to prospectively assess not only muscle mass but also grasping power and walking speed because these factors presumably reflect muscle strength more directly.

ADT might be long-lasting as a nature of the disease, increasing the prevalence of sarcopenia. Hence, prophylactic measures against sarcopenia allow for elongated treatment duration, leading to improved survival rate. For prophylaxis of sarcopenia, exercise and well-balanced nutritional intake play a pivotal role. In elderly patients, resistance exercise has been reported to stimulate protein synthesis, increasing muscle mass and strength.[33] In addition, branched-chain amino acids (BCAAs) are known to stimulate protein synthesis, and prophylactic effect of BCAA on sarcopenia has been reported in the field of nutritional science.[34,35] Currently, research into methods to combat cancer cachexia in various cancer sites has recently progressed to the combination of agents or supplements.[36] The older muscle is still able to respond to the essential amino acids and BCAAs, which have been shown to acutely stimulate muscle protein synthesis in older individuals. Thus, long-term essential amino acid supplementation may be a useful tool for the prevention and treatment of sarcopenia, particularly if excess leucine is provided in the supplement.[37] We believe that these nutritional interventions pave the way for promising prevention of sarcopenia. Although it has been yet to be reported that exercise and nutritional intervention improve a prognosis of CRPC patients, we need to conduct a large-scale prospective study to validate this hypothesis.

Conclusions

Sarcopenia is an independent predictive factor for a poor tolerance to docetaxel treatment. Given that cessation of the treatment leads to death from the disease, our study identified sarcopenia as an independent factor that raises mortality risk. In the future, we need to conduct a large-scale prospective study to validate these results.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.prnil.2018.04.002.

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