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Research Article

Relationship between body composition and hormone sensitivity for androgen deprivation therapy in patients with metastatic prostate cancer

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ABSTRACT

Background: To evaluate the relationship between body composition and the oncological outcome of androgen deprivation therapy (ADT), we investigated whether body composition features including the psoas muscle may be predictive factors of ADT.

Methods: This study enrolled patients with hormone-naïve metastatic prostate cancer who were treated with primary ADT from April 1996 to November 2013 at Kyushu University Hospital and who underwent a computed tomography scan before primary ADT for calculating body fat percentage, psoas muscle ratio (psoas muscle, cm^3/height, cm), and body mass index.

Results: Of the 178 patients enrolled, 60 patients died during follow-up. Median follow-up was 32 months, and progression-free survival and overall survival (OS) were 28 and 80 months, respectively. Multivariate analysis revealed that the psoas muscle ratio was correlated with OS (hazard ratio: 0.448; 95% confidence interval = 0.206–0.922; $p = 0.028$).

Conclusions: This study demonstrated that higher psoas muscle ratio predicts longer OS among patients with nonlocalized prostate cancer treated with primary ADT.

1. Introduction

Prostate cancer (PCa) is one of the most common cancers in men in the United States, Western Europe, and Japan.[1,2] Since the 1940s, androgen deprivation therapy (ADT) has been the gold standard for primary therapy of metastatic PCa because ADT suppresses the production of testosterone.[3] Most patients with PCa respond well to ADT because their tumors are dependent on androgens for their growth, but eventually become resistant to ADT, and are then defined as having castration-resistant PCa.[4] Clinical stage and Gleason score are important factors for predicting outcome of ADT.[5] Previously, insufficient decreases in serum testosterone levels during Luteinizing Hormone-Releasing Hormone (LHRH) agonist treatment were reported in obese men, which may detrimentally affect the outcome.[6,7] Meanwhile, there are controversial reports on the effects of obesity on the prognosis of ADT.[8–10] In addition, there are no reports on the influence of detailed body composition on the efficacy of ADT. Therefore, we hypothesized that body composition including the psoas muscle and distribution of adipose tissue may affect the efficacy of ADT, and as a result, contribute to the oncological outcome of patients with PCa.

In this study, we attempted to identify the parameters of body composition that influence the oncological outcome of ADT in PCa.

2. Materials and Methods

2.1. Study design

This study was retrospective and included patients with metastatic PCa treated with primary ADT at Kyushu University Hospital (Fukuoka, Japan) from April 1996 to November 2013. This study was approved by the institutional review board. All patients were histopathologically verified with adenocarcinoma via prostate biopsy. Body mass index (BMI) (kg/m^2) was calculated for each patient based on weight and height values recorded before therapy. All the patients were examined by computed tomography before ADT.

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Adipose tissue was identified as the pixels ranging from −250 to −50 Hounsfield units. All imaging data were transferred to a computer workstation for analysis of the visceral/subcutaneous fat (SF) and psoas muscle volume. Visceral fat (VF) volume, SF volume (Fig. 1A), psoas muscle volume (Fig. 1B) were calculated using SYNAPSE VINCENT software (Fuji Film, Tokyo, Japan). SF was calculated from the diaphragm to the pubic bone level. To calculate the visceral fat/SF ratio (V/S ratio), the VF volume was divided by the SF volume. To calculate the psoas muscle ratio, the psoas muscle volume was divided by the height. All patients were primarily treated with ADT by surgical castration or medical castration using an Luteinizing Hormone-Releasing Hormone (LHRH) agonist (goserelin acetate or leuprorelin acetate) with or without a traditional antiandrogen (bicalutamide, flutamide, or chlormadinone acetate). Progressive disease was defined as an increase in serum prostate-specific antigen (PSA) levels of >2 ng/ml and a 25% increase over the nadir, the appearance of a new lesion, or the progression of known lesions classified in accordane with the Response Evaluation Criteria in Solid Tumors.[11]

2.2. Statistical analysis

All statistical analyses were performed using JMP Pro 13 software (SAS Institute, Cary, NC, USA). Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. In multivariate analysis, we analyzed VF percentage, V/S ratio, psoas muscle ratio, and BMI separately adjusted for age, Gleason score, PSA at diagnosis, cT stage, and cM stage to investigate each parameter of body composition that may influence clinical outcome.

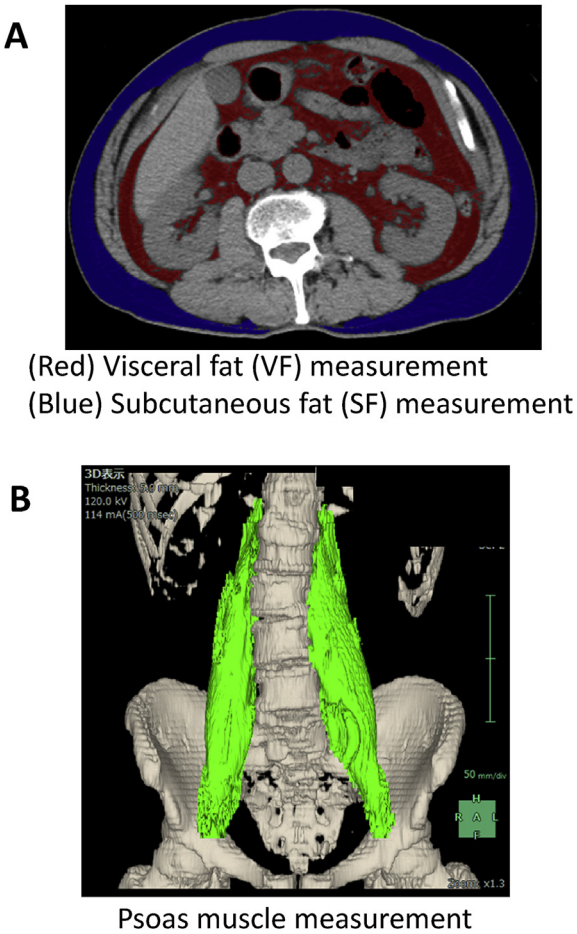

Fig. 1. Measurement of (A) visceral and subcutaneous fat and (B) psoas muscle volume using SYNAPSE VINCENT software.

3. Results

Table 1 summarizes the clinical and pathological characteristics of 178 patients. Clinical staging was undertaken before ADT, and all the patients were diagnosed with metastatic hormone-naive PCa (N1 and/or M1). Pretreatment testosterone was tested in 58 patients (32.6%). The median follow-up was 32 months (range, 0–190) and all-cause death occurred in 60 (33.7%) patients. All patients were diagnosed as having disease progression with PSA progression. Median progression-free survival (PFS) and overall survival (OS) were 28 and 80 months, respectively.

In these patients treated with ADT, we attempted to identify parameters associated with PFS and OS by univariate and multivariate analyses using the Cox proportional hazard regression model. Among several parameters, Gleason score, cT stage, cM stage, and VF percentage were identified as significant factors for PFS in univariate analysis (Table 2). Gleason score, cT stage, VF percentage, psoas muscle ratio, and BMI were revealed as significant or marginally significant factors for OS in univariate analysis (Table 2).

In this study, we focused on body composition and wanted to determine whether each parameter, such as VF percentage, V/S ratio, psoas muscle ratio, and BMI had any impact on PFS and OS considering pathological and clinical information. Therefore, we performed multivariate analysis using each of these four variables separately adjusted for age, Gleason score, PSA at diagnosis, cT

Table 1
Patient characteristics (n = 178).

variable	
Median age, years (range)	72 (46-91)
PSA at diagnosis, median (range)	164 (3.2-8740)
Biopsy Gleason score, *n* (%)	
≤6	5 (2.8)
7	29 (16.2)
≥8	129 (72.4)
not available	15 (8.4)
cT stage, *n* (%)	
T1c	1 (0.5)
T2a	4 (2.2)
T2b	5 (2.8)
T2c	1 (0.5)
T3a	64 (35.9)
T3b	43 (24.1)
T4	52 (29.2)
not available	8 (4.4)
cN stage	
N0	59 (33.1)
N1	116 (65.1)
not available	3 (1.6)
cM stage	
M0	19 (10.6)
M1	157 (88.2)
not available	2 (1.1)
Median testosterone, ng/dl (range)	400 (37-1042)
Median BMI, kg/m^2 (range)	22.5 (14.5-31.1)
Median visceral fat, % (range)	29.4 (2.1-57.6)
Median V/S ratio, ratio (range)	1.16 (0.34-19.6)
Psoas muscle ratio, ratio (range)	1.95 (0.71-3.64)
hormonal therapy	
Castration	11 (6.2)
Combined androgen blockage	167 (93.8)

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen; V/S ratio, Visceral fat/subcutaneous fat ratio.
Psoas muscle ratio: Psoas muscle/height (cm^3/cm).

Table 2
Univariate analysis of metastatic PCa.

Variate	No.	Progression-free survival			Overall survival		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Age (per 1 year)							
		1.002	0.976-1.029	0.850	1.014	0.979-1.051	0.439
Gleason score							
≤6	5	1			1		
7	29	9.49 E+08	0.980-infinity	0.052	3.97 E+08	0.569-infinity	0.130
≥8	129	1.70 E+09	1.840-infinity	0.008	5.80 E+08	0.899-infinity	0.062
PSA at diagnosis (per 1 ng/ml)							
		1	0.999-1.000	0.128	1	0.999-1.000	0.237
cT stage							
T1c T2a T2b T2c	11	1			1		
T3a T3b	107	1.802	0.664-7.405	0.277	4.73 E+08	1.543-infinity	0.015
T4	52	3.392	1.221-14.082	0.015	7.56 E+08	2.432-infinity	0.003
cN stage							
N0	59	1			1		
N1	116	1.443	0.939-2.277	0.095	1.104	0.646-1.941	0.720
cM stage							
M0	19	1			1		
M1	157	2.365	1.125-6.079	0.020	2.111	0.856-7.032	0.112
Testosterone (per 1 ng/dl)		1.001	0.998-1.003	0.388	1.001	0.998-1.004	0.442
Visceral fat percentage (per 1%)		0.979	0.965-0.994	0.006	0.979	0.961-0.997	0.029
V/S ratio (per 1)		1.010	0.975-1.029	0.446	1.009	0.921-1.038	0.722
Psoas muscle ratio (per 1 cm^3/cm)		1.109	0.729-1.651	0.901	0.593	0.316-1.066	0.082
BMI (per 1 kg/m2)		0.943	0.881-1.007	0.084	0.883	0.802-0.968	0.007

Abbreviations: BMI, body mass index;PSA, prostate-specific antigen; V/S ratio, Visceral fat/subcutaneous fat ratio.

Table 3
Multivariate analysis of metastatic PCa.

Variate	No.	Progression-free survival			Overall survival		
		HR[a]	95% CI[a]	*p* value	HR[a]	95% CI[a]	*p* value
Visceral fat percentage (per 1%)		0.990	0.973-1.006	0.238	0.992	0.221-2.258	0.544
V/S ratio (per 1)		1.004	0.980-0.029	0.714	1.003	0.958-1.049	0.899
Psoas muscle ratio (per 1 cm^3/cm)		1.035	0.642-1.630	0.882	0.448	0.206-0.922	0.028
BMI (per 1 kg/m2)		0.972	0.904-1.043	0.441	0.915	0.823-1.013	0.091

Abbreviations: BMI, body mass index; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen.
[a] Adjusted for age, GS, PSA at diagnosis, cT stage and cM stage.

stage, and cM stage. As a result, psoas muscle ratio was significantly associated with OS (hazard ratio = 0.448; 95% confidence interval (CI) = 0.206–0.922; $p = 0.028$) (Table 3).

Finally, we investigated the relationship between serum testosterone levels and psoas muscle ratio. Serum testosterone data were available for 58 patients. The correlation coefficient was low, but the psoas muscle ratio was positively correlated with serum testosterone before ADT treatment (R = 0.293; $p = 0.0001$; Fig. 2).

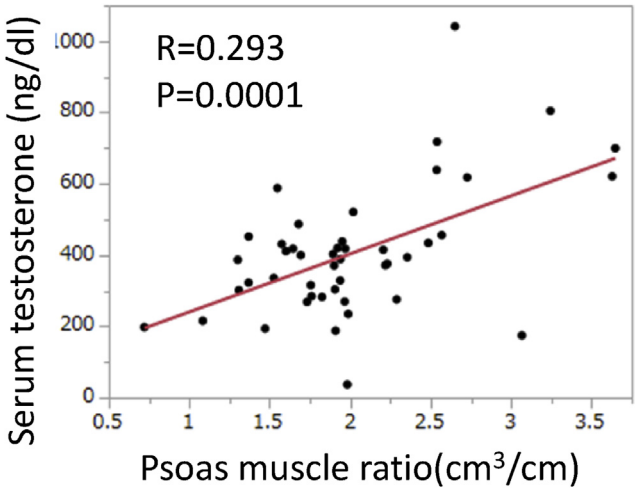

Fig. 2. Relationship between serum testosterone (ng/dl) and psoas muscle ratio (cm^3/cm).

4. Discussion

Numerous epidemiological studies have examined the relationship between BMI and PCa incidence, but the findings remain inconclusive.[12,13] Obesity increases the risk of high-grade PCa.[13] However, higher BMI is a good prognostic factor in patients with androgen-dependent metastatic PCa[14] and reduces the risk of metastasis after radical prostatectomy.[15] Obese patients tend to be medicated for diabetes (e.g., metformin), which might have some antitumor effects.[16] In a multivariate analysis in our study, BMI was not significant but showed a good tendency in OS (HR = 0.915; 95% CI: 0.823–1.013; $p = 0.091$). In our study cohort, median BMI was 22.5 and almost the same as the older Japanese population.[17] Among Japanese adults aged 65 and older, a lower BMI was a risk factor of all-cause mortality, and our BMI results may support the speculation that having a thin body increases the risk of mortality.

Intriguingly, higher muscle strength is reported to be associated with improved survival in older patients with advanced cancer including PCa.[18] In line with this notion, to our knowledge, this is the first study to show that increased muscle volume was associated with prognosis in ADT. We also demonstrated that the psoas muscle ratio was correlated with serum testosterone level.

Testosterone has a critical role in PCa development and progression, and many studies have investigated the relationship between serum testosterone levels and PCa. Low testosterone is associated with high Gleason score[19-21] and higher pathological stage.[22,23] Before ADT, higher testosterone levels in advanced PCa are correlated with prolonged OS.[24] For Japanese patients, testosterone reduction (≥480 ng/dl) during ADT therapy is a significant prognostic factor for OS.[25] We focused on the psoas muscle because it is a core muscle and is considered to reflect the general health and mortality of different diseases.[26-28] In healthy men, serum testosterone levels have a positive correlation with lean body mass[29] and muscle strength.[30] Furthermore, control of serum testosterone by Gonadotropin releasing hormone (GnRH) agonist and testosterone administration positively affects muscle size and strength.[31] Consistent with this, our study suggested that the psoas muscle is a predictive marker of serum testosterone levels. Because high testosterone levels in serum is a well-known factor of OS[9], the psoas muscle may be associated with OS via serum testosterone levels. However, in univariate analysis, serum testosterone was not a significant predictor of OS. This study included 178 patients, but serum testosterone data were only available for 58 patients, and hence we could not show a significant association with oncological outcome. Furthermore, other factors may be involved in better prognosis among men with larger psoas muscle volumes, and this area warrants further research.

ADT has numerous side effects including loss of libido, cardiovascular disease, osteoporosis, metabolic syndrome, and sarcopenia.[32] Sarcopenia is a risk factor of frailty and falls[33] and leads to reduced quality of life. To prevent the side effects of ADT and for better quality of life, exercise should be recommended.[34,35] In addition, this study supported the hypothesis that exercise may improve the outcome of ADT via an increase in psoas muscle. However, it is inconclusive as to whether exercise can extend OS in patients who received ADT treatment, and more research is required.

Our study is not devoid of limitations. This is a retrospective study, and the patient number was relatively small. In addition, data on serum testosterone were available for only 58 patients (32.6%).

In conclusion, we showed that the psoas muscle ratio is a good prognostic factor of OS in patients with metastatic PCa and can be mediated by serum testosterone levels.

Conflicts of interest

The authors declare no conflict of interest.

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