Research Article

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

Eiji Kashiwagi, Masaki Shiota*, Hiroyuki Masaoka, Kenjiro Imada, Keisuke Monji, Ario Takeuchi, Junichi Inokuchi, Katsunori Tatsugami, Masatoshi Eto

Department of Urology, Graduate School of Medical Sciences, Kyushu University, Japan

ARTICLE INFO

Article history:
Received 19 September 2019
Received in revised form 5 November 2019
Accepted 14 November 2019
Available online 30 November 2019

Keywords:
Androgen deprivation therapy
Body composition
Prostate cancer
Psoas muscle
Testosterone

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-naive 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, cm³/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.

© 2019 Asian Pacific Prostate Society, Published by Elsevier Korea LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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.1 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.3 Clinical stage and Gleason score are important factors for predicting outcome of ADT.4 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.5,6 Meanwhile, there are controversial reports on the effects of obesity on the prognosis of ADT.7,8 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/m²) was calculated for each patient based on weight and height values recorded before therapy. All the patients were examined by computed tomography before ADT.

* Corresponding author. Department of Urology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: shiota@uro.med.kyushu-u.ac.jp (M. Shiota).

https://doi.org/10.1016/j.prnil.2019.11.002
©2019 Asian Pacific Prostate Society, Published by Elsevier Korea LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 accordance with the Response Evaluation Criteria in Solid Tumors.11

2. 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 stage, and cM stage to investigate each parameter of body composition that may influence clinical outcome.

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 stage, and cM stage to investigate each parameter of body composition that may influence clinical outcome.

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

| variable | Median age, years (range) | PSA at diagnosis, median (range) | Biopsy Gleason score, n (%) |
|----------|--------------------------|-------------------------------|-----------------------------|
| ≤6       | 69 (46-91)               | 164 (3.2-8740)               | 5 (2.8)                    |
| 7        | 29 (16.2)                | 129 (72.4)                   | 15 (8.4)                   |
| ≥8       |                         |                              |                            |
| 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 | 59 (33.1)                | 116 (65.1)                   | 3 (1.6)                    |
| M0       | 19 (10.6)                | 157 (88.2)                   | 2 (1.1)                    |
| M1       | 400 (37-1042)            | 225 (145-311)                |                            |
| Median visceral fat, % (range) | 29.4 (2.1-57.6) | 1.16 (0.34-19.6) | 1.95 (0.71-3.64) |
| Psoas muscle ratio, ratio (range) | 10.6 (1.0-5.6) | 1.16 (0.34-19.6) | 1.95 (0.71-3.64) |
| hormonal therapy |                  |                              |                            |
| Castration | 11 (6.2)                |                              |                            |
| Combined androgen blockage | 167 (93.8) | 1.95 (0.71-3.64) |                            |

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen; V/S ratio, Visceral fat/subcutaneous fat ratio. Psoas muscle ratio: Psoas muscle/height (cm²/cm).
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).

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.

---

**Table 2**

| 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                  |     | \( \leq 6 \) | 5 | 1 | 1 | \( > 7 \) | 29 | 9.49-08 0.980-infinity | 0.052 | 3.97-08 0.569-infinity | 0.130 |
|                                |     | \( \geq 8 \) | 129 | 1.70-09 1.840-infinity | 0.008 | 5.80-08 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 | 4.73-08 1.543-infinity | 0.015 |
|                                |     | T4 | 52 | 3.392 | 1.221-14.082 | 0.015 | 7.56-08 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 |
| V/S ratio (per 1)              |     | 0.979 | 0.965-0.994 | 0.006 | 0.979 | 0.961-0.997 | 0.029 |
| Psoas muscle ratio (per 1 cm\(^3\)/cm) |     | 1.109 | 0.720-1.631 | 0.901 | 0.593 | 0.316-1.066 | 0.082 |
| BMI (per 1 kg/m\(^2\))         |     | 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**

| Variate                        | No. | Progression-free survival | Overall survival |
|--------------------------------|-----|----------------------------|------------------|
|                                |     | HR | 95% CI | \( p \) value | HR | 95% CI | \( p \) 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 | 0.980-0.999 | 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/m\(^2\))         |     | 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.

---

**Fig. 2**. Relationship between serum testosterone (ng/dl) and psoas muscle ratio (cm\(^3\)/cm).
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 and higher pathological stage. Before ADT, higher testosterone levels in advanced PCa are correlated with prolonged OS. For Japanese patients, testosterone reduction (>480 ng/dl) during ADT therapy is a significant prognostic factor for OS. 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. In healthy men, serum testosterone levels have a positive correlation with lean body mass and muscle strength. Furthermore, control of serum testosterone by Gonadotropin releasing hormone (GnRH) agonist and testosterone administration positively affects muscle size and strength. 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, 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. Sarcopenia is a risk factor of frailty and falls and leads to reduced quality of life. To prevent the side effects of ADT and for better quality of life, exercise should be recommended. 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 with metastatic prostate cancer and the SRD5A2 polymorphism. Prostate Cancer Prostatic Dis 2016;19(2):191.

The authors thank H. Nikki March, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References
1. Wong MC, Goggins WB, Wang IH, Fung FD, Leung C, Wong SY, et al. Global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. Eur Urol 2016;70(5):662–74.
2. Kimura T, Takahashi H, Okaya M, Kudo M, Inaba H, Kuruma H, et al. Time trends in histological features of latent prostate cancer in Japan. J Urol 2016;195(5):1415–20.
3. Huggins C, Hodges CV. Studies on prostatic cancer: 1. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. J Urol 2002;168(1):9–12.
4. Shiota M, Yoshimura A, Naito S. Pro-survival and anti-apoptotic properties of androgen receptor signaling by oxidative stress promote treatment resistance in prostate cancer. Endocr Relat Cancer 2012;19(6):243–53.
5. Ross RW, Xie W, Regan MM, Pomerantz M, Nakabayashi M, Daskivich TJ, et al. Efficacy of androgen deprivation therapy (ADT) in patients with advanced prostate cancer: association between Gleason score, prostate-specific antigen level, and prior ADT exposure with duration of ADT effect. Cancer 2008;112(6):1247–53.
6. Oefelein MG, Corrnan R. Failure to achieve castrate levels of testosterone during luteinizing hormone releasing hormone agonist therapy: the case for monitoring serum testosterone and a treatment decision algorithm. J Urol 2010;184(3):726–9.
7. Smith MR. Obesity and sex steroids during gonadotropin-releasing hormone agonist treatment for prostate cancer. Clin Cancer Res 2007;13(1):241–5.
8. Kato C, Aromon WJ, Terriss MK, Presto JC, Kane JC, Ambling CL, et al. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. BJU Int 2012;110(4):492–8.
9. Shiota M, Takeuchi A, Sugimoto M, Kashiwagi E, Dejima T, Kiyoshima K, et al. Prostate Specific Impact of Serum Testosterone and Body Mass Index Before Androgen-deprivation Therapy in Metastatic Prostate Cancer. Anticancer Res 2015;35(12):6925–32.
10. Shiota M, Fujimoto N, Yokomizo A, Takeuchi A, Kashiwagi E, Dejima T, et al. The prognostic impact of serum testosterone during androgen-deprivation therapy in patients with metastatic prostate cancer and the SRD5A2 polymorphism. Prostate Cancer Prostatic Dis 2016;19(2):191.
11. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26(7):1148.
12. Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, et al. Prospective study of adipose tissue and weight change in relation to prostate cancer incidence and mortality. Cancer 2007;109(4):675–84.
13. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi H, Hsing AW, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomark Prev 2006;15(10):1977–83.
14. Montgomery RB, Goldman B, Tangen CM, Hussain M, Petrylak DP, Page S, et al. Association of body mass index with response and survival in men with metastatic prostate cancer: Southwest Oncology Group Trials 8899 and 9916. J Urol 2007;178(5):1946–51.
15. Schiffman J, Karakiewicz PI, Rink M, Malkin L, Salomon G, Tiliki D, et al. Obesity paradox in prostate cancer: increased body mass index was associated with decreased risk of metastases after surgery in 13,667 patients. World J Urol 2018;36:1067–72.
16. Raval AD, Thakker D, Vyas A, Salkini M, Madhavan S, Sambamoorthi U. Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2015;18(2):110–21.
17. Tamakoshi A, Yatsuya H, Lin Y, Tamakoshi K, Kondo T, Suzuki S, et al. BMI and all-cause mortality among Japanese older adults: findings from the Japan collaborative cohort study. Obesity 2010;18(2):362–9.
18. Versteeg KS, Blauwbluff-Buskermolen S, Buffart LM, de van der Schueren MA, E. Kashiwagi et al. / Psoas muscle and ADT for prostate cancer 25
19. Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. Urology 2008;72(6):1240–5.
20. San Francisco IF, Regan MM, DeWolf WC, Olumi AF. Low age adjusted free testosterone levels correlate with poorly differentiated prostate cancer. J Urol 2006;175(4):1341–6.
21. Schatzl G, Madersbacher S, Thurisdal T, Waldmüller J, Kramer G, Haitel A, et al. High grade prostate cancer is associated with low serum testosterone levels. The Prostate 2001;47(1):52–8.
22. Isom-Batz G, Bianco Jr. JF, Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. J Urol 2005;173(6):1935–7.
23. Imamoto T, Suzuki H, Fukasawa S, Shimbo M, Inahara M, Komiya A, et al. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. Eur Urol 2005;47(3):308–12.
24. Claps M, Petrelli F, Caffo O, Amoroso V, Roca E, Mosca A, et al. Testosterone levels and prostate cancer prognosis: A systematic review and meta-analysis. Clin Genitourin Cancer 2018;16(3):165–75.
25. Yamamoto S, Sakamoto S, Minnui X, Tamura T, Otsuka K, Sato K, et al. Testosterone reduction of > 480 ng/dl predicts favorable prognosis of Japanese men with advanced prostate cancer treated with androgen-deprivation therapy. Clin Genitourin Cancer 2017;15(6):e1107–15.
26. Pahor M, Mannini T, Mj-Jton Cesa, Health, Aging. Sarcoepenia: clinical evaluation, biological markers and other evaluation tools. J Nutr Health Aging 2009;13(8):724–8.
27. Souto AB, Deol AM, Yu H, Boyd B, Matthews J, Wallen EM, et al. Sarcoepenia as a predictor of complications and survival following radical cystectomy. J Urol 2019;114(6):714–20.
28. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcoepenia and mortality after liver transplantation. J Am Coll Surg 2010;211(2):271–8.
29. Vermeulen A, Goemaere S, Kaufman J. Testosterone, body composition and aging. J Endocrinol Invest 1999;22(3 Suppl):110–6.
30. Roy TA, Blackman MR, Harman SM, Tobin JD, Schrager M, Metter EJ. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. Am J Physiol Endocrinol Metab 2002;283(2):E284–94.

31. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, et al. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 2001;281(6):E1172–81.

32. Isbarn H, Boccon-Gibod L, Carroll PR, Montorsi F, Schulman C, Smith MR, et al. Androgen deprivation therapy for the treatment of prostate cancer: consider both benefits and risks. Eur Urol 2009;55(1):62–75.

33. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–57.

34. Galvão D, Taaffe D, Spry N, Newton R. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. Prostate Cancer Prostatic Dis 2007;10(4):340–6.

35. Keogh JW, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. J Pain Symptom Manag 2012;43(1):96–110.