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The fat body mass increase after adjuvant androgen deprivation therapy is predictive of prostate cancer outcome

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Abstract

Androgen deprivation therapy (ADT) leads to important changes in body composition. No data are currently available about the relationship between these treatment-related changes and patient outcome. Using dual-energy X-ray absorptiometry, bone mineral density (BMD), fat body mass (FBM), and lean body mass (LBM) were determined at baseline, and after 1 and 2 years in 53 non-metastatic prostate cancer (PC) patients with high-risk disease treated with adjuvant ADT. Changes in these parameters were correlated with patient outcome in terms of adverse skeletal events, disease recurrence, and overall survival. ADT led to a significant decrease in BMD ($p < 0.03$) and LBM ($p < 0.03$), and an increase in FBM, ($p < 0.0001$). Changes in BMD failed to show any relationship with time to skeletal-related events (SRE), disease recurrence, and death. FBM increase was a significant predictor of higher risk of SRE [hazard ratio (HR) 3.024, 95 % CI 1.004–10.353, $p < 0.02$], higher risk of death (HR 2.373, 95 % CI 1.012–5.567, $p = 0.04$), and a non-significant higher risk of disease recurrence (HR 2.219, 95 % CI 0.956–5.150, $p = 0.13$). LBM decrease did not correlate with either time to SRE or survival, while a non-significant association with disease recurrence (HR 1.550, 95 % CI 0.670–3.605, $p = 0.06$) was observed. The early increase in FBM may provide predictive information of poor outcome in PC patients given ADT. These data suggest that the adoption of early preventive measures aiming to reduce fat increase can potentially reduce the morbidity and mortality risk.

Keywords

Prostatic neoplasm Androgens Body composition Prognosis

Introduction

Androgen deprivation therapy (ADT) is the mainstay of treatment of patients with advanced prostate cancer (PC). This treatment is also frequently prescribed as adjuvant approach in the management of non-metastatic high-risk patients after local regional treatments, (radical prostatectomy and/or radiation therapy) and in non-metastatic patients with biochemical progression. In these two settings, the ADT duration may be of many years [1]. Long-term ADT may induce profound changes in body composition such as decreased bone mineral density (BMD), decreased lean body mass (LBM), and increased fat body mass (FBM).

These changes put the patient to an increased risk of osteoporosis, metabolic syndrome, diabetes, and cardiovascular diseases [2].

Obesity in men undergoing ADT is not only associated with greater risk of cardiovascular disease but also with a higher risk of biochemical recurrence after radical prostatectomy [3, 4], higher risk of castration-resistant disease and metastasis [5], and higher PC-specific mortality [6, 7].

The mechanisms by which obesity could affect the tumor biology are increased serum insulin levels that are notoriously a growth factor [8, 9], altered adipokine and cytokine production, and increased levels of pro-inflammatory mediators [10].

Dual X-ray absorptiometry (DXA) is a reliable and accurate method to determine the changes in body composition in PC patients undergoing ADT [11–13]. While the decrease in BMD is known to be associated with increased risk of bone fracture [14, 15], the impact of changes in FBM during ADT on patient outcome has never been explored.

We have conducted a prospective cohort study to evaluate the changes in body composition as measured with the DXA scan in PC patients submitted to adjuvant ADT [11]. All these patients were subsequently followed up for a long time period. The present study was undertaken to provide explorative information on the relationship between changes in FBM and patient's overall survival (OS). In addition, since progression-free survival (PFS) and adverse skeletal-related event (SREs) are also relevant end points, we evaluated as secondary end points the relationship between changes in FBM and either time to skeletal-related events (TTSRE) or PFS, and explored whether changes of BMD and LBM were associated with OS, PFS, and TTSRE.

Patients and methods

Patients

The study involved patients with PC without apparent bone metastases who were judged eligible for ADT. They were recruited between 1997 and 2001 at the Prostate Cancer Unit of San Luigi Gonzaga Hospital in Orbassano, Italy. To be enrolled in the study, the patients had a histological diagnosis of PC, a survival prospect of more than 6 months, and absence of metastasis as assessed by bone scan and CT scan. Exclusion criteria were concomitant metabolic bone disease, primary hyperparathyroidism or chronic hypercortisolism, renal failure (serum creatinine <1.5 mg/dl), and prior or concomitant treatment with bisphosphonates or other drugs known to affect bone metabolism.

Pre-treatment evaluation included tumor stage, routine blood chemistry, and assessment of serum PSA.

Methods

BMD was evaluated by DXA at lumbar spine, using Hologic QDR-4500W instrumentation. The area BMD (g/cm^2) at the spine (L2–L4), and the bone mineral content (g), LBM (g) and FBM (g), were calculated using standard software. More details about the DXA measurements, precision, and calibration were described in a previously published paper [11].

DXA measurements were performed before starting ADT, after 1 and 2 years. Data were analyzed using absolute values of BMD (g/cm^2), FBM (g), and LBM (g). Whole-body bone scanning was performed within 2 months of patient enrollment in the study and positive hot spots were confirmed by radiology (X-ray and or CT scan). In cases of bone metastasis, patient was excluded from the study.

OS was defined as the time from the start of ADT to death or last follow-up. PFS was defined as the time elapsing from the start of ADT to a 50 % increase in the PSA values versus the lowest PSA values obtained during hormonal treatment (nadir) and/or occurrence of new lesion. TTSRE was defined as the time from the start of hormonal therapy to the first SRE, defined as pathological fractures (including vertebral fractures), spinal cord compression, and/or orthopedic surgery. Data for patients who survived and for those surviving without disease progression or without the occurrence of SREs were censored at the date of the last follow-up visit.

Statistical analysis

The prognostic role of BMD, LBM, and FBM in terms of TTSRE, PFS, and OS was assessed at baseline or as an absolute difference between baseline and 1 year (1 year value − baseline value) of ADT. Either baseline values or the absolute difference between the 2 time points were categorized at the median value. In this unplanned post hoc analysis, the 53 patients enrolled provided a potency of 80 % of detecting an absolute difference of 35 % (from 50 to 85 %) at 5 year in terms of OS, TTSRE, or PFS, with a fixed alpha error of 0.05. OS, TTP, and TTSRE curves were calculated with the Kaplan–Meier method and comparison between groups was assessed by the log-rank test. The estimation of the hazard ratio (HR) of the parameters of body composition (dichotomized at the median values) on outcome measures was determined using Cox regression analysis. Statistical computations were performed using the SPSS package for Windows (version 17.0). Statistical significance was set at $p < 0.05$.

Results

This study population comprised 35 patients with non-metastatic PC included in a previous study [11], plus additional 18 consecutive patients meeting the inclusion criteria that were observed in the same period. The demography and characteristics of the 53 patients prospectively enrolled are shown in Table 1. The median age was 71 years (range 44–83). Forty-five patients (84.9 %) had AUA stage B and C, 8 patients stage D1 (15.1 %). According to the National Comprehensive Cancer Network (NCCN) classification [16], 37 patients (70 %) were classified with high-risk disease as assessed by Gleason score >7 and or PSA >20 and or locally advanced plus/minus N-positive disease, while 16 (30 %) had intermediate risk disease. All patients were initially submitted to local regional therapies with radical intent, 16 of them (30.2 %) received radical prostatectomy, 27 (50.9 %) radiation therapy, and 10 (18.9. %) received both radical prostatectomy and radiation therapy. Adjuvant therapy consisted of LHRH-A alone. Bicalutamide was added to LHRH-A during the first 6 weeks to prevent the tumor flare and then interrupted. Adjuvant LHRH-A was never stopped in 40 patients, while it was interrupted in the remaining 13 after 3–4 years.

Table 1

Patients' characteristics

No. of patients	53
Median age (range)	73 (44–83)
No disease stage (%)	
AUA TNM	
B, C T2–T3 N0	45 (84.9)
D T2–T3 N1	8 (15.1)
PSA (No, %)	
PSA ≤ 10	16 (30.2)
10 < PSA ≥ 20	10 (18.9)
PSA > 20	24 (45.3)
Missing	3 (5.6)
Gleason score (No, %)	
GS < 7	10 (18.9)
GS = 7	22 (41.5)
GS > 7	17 (32.1)
Missing	4 (7.5)
Previous local regional therapies	
Radical prostatectomy	16 (30.2 %)
Radiation therapy	27 (50.9 %)
Both prostatectomy and radiation therapy	10 (18.9 %)
Median height, cm (range)	167 (60–180)
Median weight, kg (range)	76 (50–105)
Median BMI kg/m^2(range)	25 (19–39)

Effects of androgen deprivation therapy on body composition

A progressive, significant decrease in BMD was observed at the lumbar spine after ADT. BMD (g/cm^2) at lumbar spine [mean, 95 % confidence interval (CI)] was 0.943 (0.874–1.013) at baseline condition, 0.933 (0.866–1.00) after 1 year, and 0.927 (0.863–0.991) after 2 years ($p < 0.03$). LBM (g) also decreased during ADT; mean (95 % CI): 50,216 (48,068–52,364), 49,553 (47,314–51,791), and 49,377 (47,247–51,507), at baseline, 1 and 2 years, respectively, ($p < 0.03$). Conversely, FBM (g) consistently increased, mean (95 % CI): 19,463 (17,143–21,783), 21,028 (18,964–23,093), and 21,680 (19,427–23,932), respectively, ($p < 0.0001$) (Table 2).

Table 2

Changes in bone mineral density, total fat body mass, and total lean body mass after androgen deprivation therapy

	Baseline	**1 year**	**2 years**	***p* value**
Bone mineral density L2–L4 (g/cm^2)				
Mean (95 % CI)	0.943 (0.874–1.013)	0.933 (0.866–1.00)	0.927 (0.863–0.991)	$p < 0.03$
Fat body mass (g)				
Mean (95 % CI)	19,463 (17,143–21,783)	21,028 (18,964–23,093)	21,680 (19,427–23,932)	$p = 0.00$
Lean body mass (g)				

	Baseline	1 year	2 years	*p* value
Mean (95 % CI)	50,216 (48,068–52,364)	49,553 (47,314–51,791)	49,377 (47,247–51,507)	$p < 0.03$

Prognostic role of body composition at baseline

After a median follow-up of 76 months, 11 patients (22.0 %) underwent adverse SRE, 20 (40.0 %) had PSA progression, and 22 patients (44.0 %) died.

High FBM (above the median) at baseline condition did not show any significant relationship with TTSRE (HR 1.356, 95 % CI 0.481–3.822; $p = 0.565$), TTP (HR 1.265, 95 % CI 0.580–2.760, $p = 0.554$), and OS (HR 0.661, 95 % CI 0.306–1.429). Similarly, low LBM and BMD (below the median) failed to show any relationship with TTSRE [(HR 0.909, 95 % CI 0.327–2.528, $p = 0.854$) and (HR 0.795, 95 % CI 0.287–2.204, $p = 0.659$)], TTP [(HR 1.517, 95 % CI 0.685–3.363, $p = 0.304$) and (HR 1.096, 95 % CI 0.506–2.374; $p = 0.815$)], and OS [(HR 1.114, 95 % CI 0.511–2.431; $p = 0.786$) and (HR 1.407, 95 % CI 0.490–2.238; $p = 0.906$), respectively].

Prognostic role of changes in body composition during the first year of treatment

The FBM increase during the first year was significantly associated with a higher risk of death (HR 2.373, 95 % CI 1.012–5.567, $p = 0.04$) and SRE (HR 3.024, 95 % CI 1.004–10.353, $p = 0.02$). It was also associated with a higher risk of disease progression (HR 2.219, 95 % CI 0.956–5.150, $p = 0.13$) without attaining the statistical significance (Fig. 1).

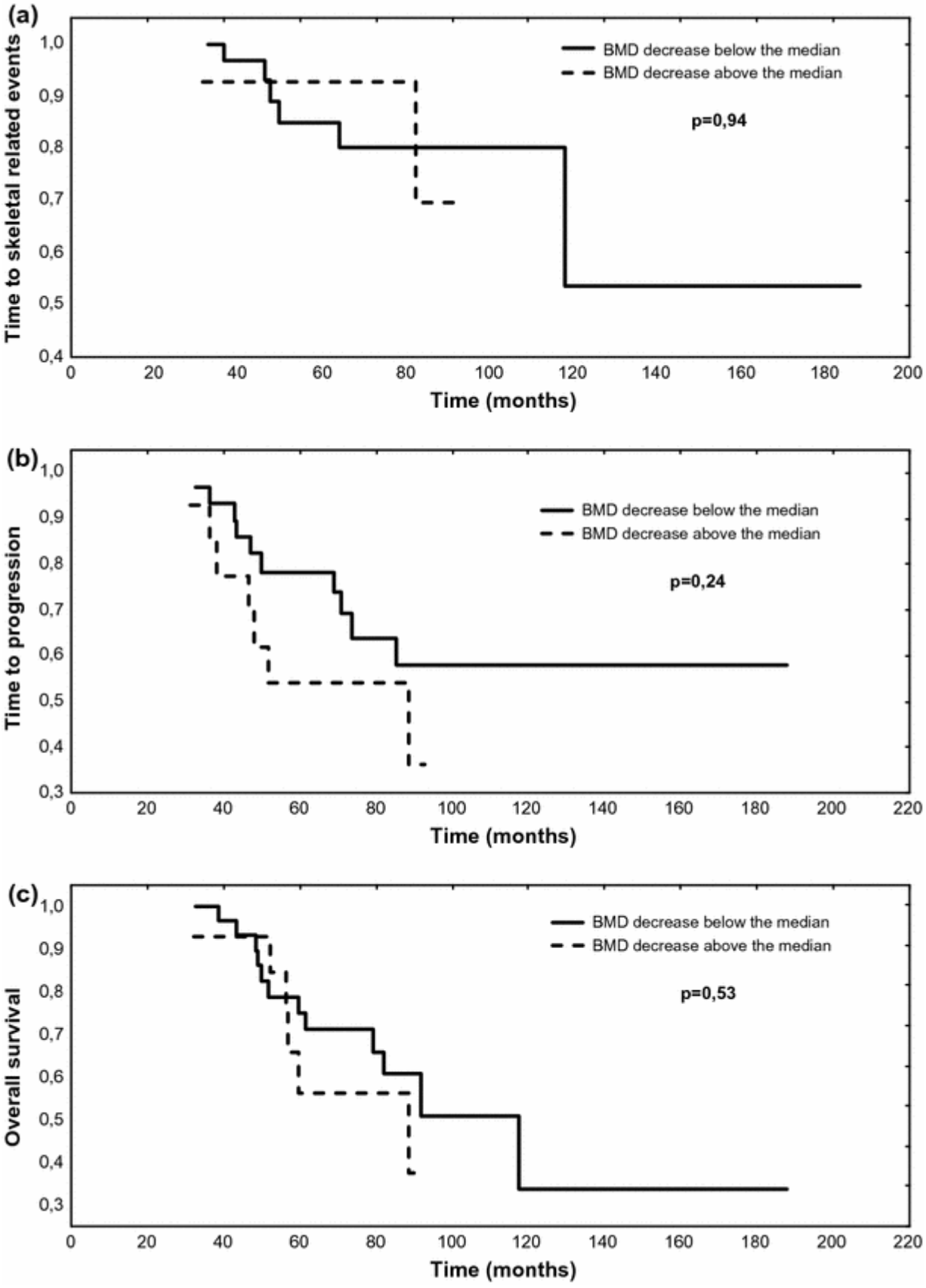

Fig. 1

Effects of changes in bone mineral density (BMD) on patient outcome in terms of time to skeletal-related events (**a**), progression-free survival (**b**), and overall survival (**c**)

The decrease in BMD failed to show any significant relationship with time to SRE onset (HR 1.084, 95 % CI 0.280–4.199, $p = 0.9$), disease recurrence (HR 1.491, 95 % CI 0.624–3.558, $p = 0.24$), and death (HR 1.380, 95 % CI 0.554–3.438, $p = 0.53$) (Fig. 2).

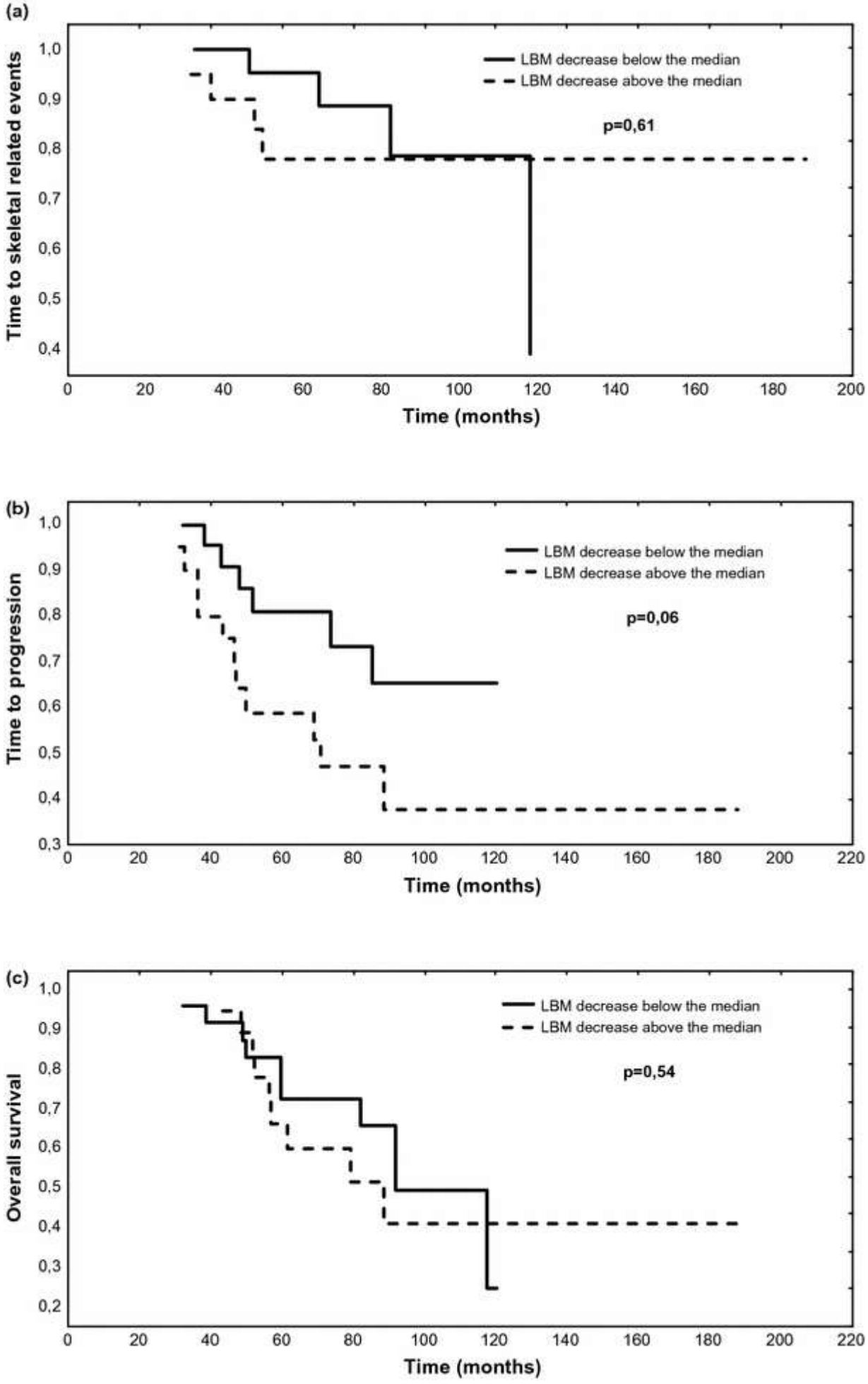
(a)
Time to skeletal related events
1,0
0,9
0,8
0,7
0,6
0,5
0,4
LBM decrease below the median
LBM decrease above the median
p=0,61
0
20
40
60
80
100
120
140
160
180
200
Time (months)
(b)
Time to progression
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
LBM decrease below the median
LBM decrease above the median
p=0,06
0
20
40
60
80
100
120
140
160
180
200
220
Time (months)
(c)
Overall survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
LBM decrease below the median
LBM decrease above the median
p=0,54
0
20
40
60
80
100
120
140
160
180
200
220
Time (months)

Fig. 2

Effects of changes in lean body mass (LBM) on patient outcome in terms of time to skeletal-related events (**a**), progression-free survival (**b**), and overall survival (**c**)

LBM decrease did not correlate with either TTSRE (HR 1.151, 95 % CI 0.350–3.784, $p = 0.61$) or OS (HR 1.291, 95 % CI 0.558–2.987, $p = 0.54$), while was predictive for higher risk of disease recurrence, without attaining the statistical significance (HR 1.555, 95 % CI 0.670–3.605, $p = 0.06$) (Fig 3).

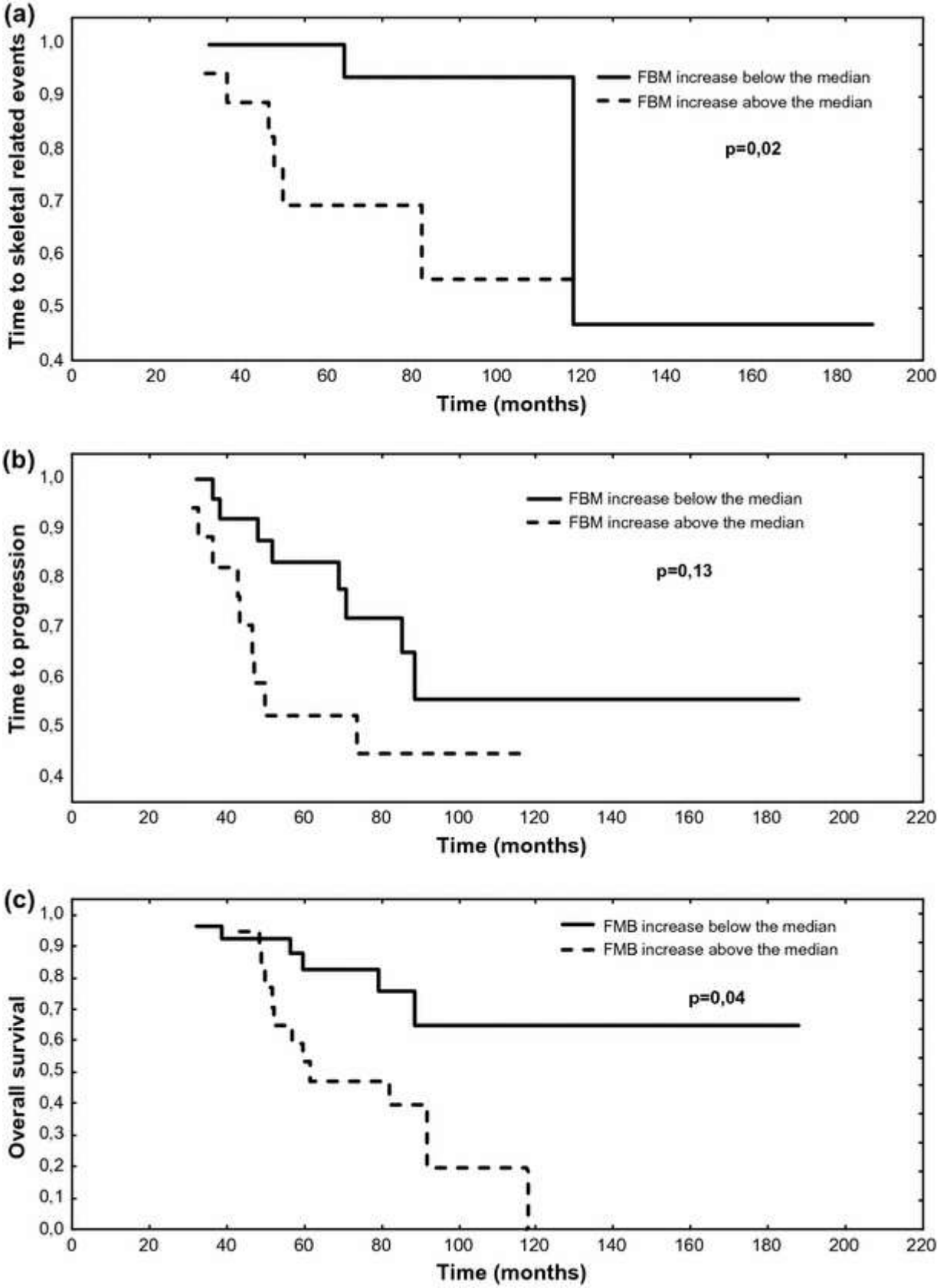

Fig. 3

Effects of changes in fat body mass (FBM) on patient outcome in terms of time to skeletal-related events (**a**), progression-free survival (**b**) and overall survival (**c**)

Prognostic role of changes in body composition during the second year of treatment

We also evaluated whether further changes of body composition between 1 and 2 years of ADT can influence the patients outcome. None of the three variables analyzed were predictor of patients outcome. FBM increase above the median in the second year of treatment failed to show any relationship with TTSRE (HR 0.959, 95 % CI 0.239–3.838, $p = 0.952$), TTP (HR 1.407, 95 % CI 0.487–4.046, $p = 0.578$), and OS (HR 0.800, 95 % CI 0.308–2.077, $p = 0.646$. The HR of BMD decrease was 0.341 (95 % CI 0.069–1.689, $p = 0.187$) for TTSRE, 1.001 (95 % CI 0.350–2.862, $p = 0.998$) for PFS, and 0.835 (95 % CI 0.317–2.199, $p = 0.716$) for OS, respectively. LBM decrease below the median during the second year did not correlate with either TTSRE (HB 1.768, 95 % CI 0.414–7.548, $p = 0.442$), or PFS (HR 1.197, 95 % CI 0.414–3.458, $p = 0.740$) or OS (HR 1.037, 95 % CI 0.395–2.723, $p = 0.940$).

Discussion

The long-term consequences of ADT in PC patients can impair the patient quality of life and increase the risk of mortality. In a meta-analysis, the decrease in PC-specific mortality induced by ADT was in part counterbalanced by an increased risk for non-PC-specific mortality [17].

The change in body composition is a major determinant of increased morbidity and mortality induced by ADT [7], and DXA provides the most precise measure of body composition.

The occurrence of metabolic syndrome may increase the risk of death due to cancer-unrelated causes [17–19]. In addition, recent data suggest that obesity is associated with increased risk of aggressive disease [20] and poor prognosis [5–7].

In this series, FBM assessed at baseline failed to be associated with prognostic information; however, the FBM increase after ADT was a significant predictor of higher risk of death and this is a relevant and an original finding.

Androgen receptors are present on visceral adipocytes [21], and it is likely that testosterone is directly involved in the mobilization of fatty acids. The deep reduction in serum testosterone levels by gonadotropin release hormone agonist increases the fasting plasma insulin levels, cholesterol, and triglycerides, and decrease insulin sensitivity [19]. The increase of FBM and the changes in lipid profile due to ADT, can lead to the metabolic syndrome, increasing the risk of cardiovascular disease, dyslipidemia, diabetes mellitus, hypertension, and stroke [17–19, 22].

In our study, FBM increase was also related to a higher although not significant risk of disease progression (HR 2.219, 95 % CI 0.956–5.150, $p = 0.13$). As mentioned in the Patients and Methods section, the low number of patients enrolled in this study confers a potency to detect only a great

difference of outcome events between groups, so this observation does not exclude a role of FBM increase in favoring a greater aggressiveness of the disease, thus impairing the efficacy of ADT.

Noteworthy, although FBM progressively increased between the 1st year and the 2nd year of ADT, the changes in FBM beyond the 1st year failed to be associated with prognosis and increase risk of SRE. These data suggest that early changes may have a major effect on patient outcome and this observation may have an impact on the timing to adopt preventive measures.

Interestingly, increased FBM after ADT was also significantly associated with an increased risk of SREs and this is an unexpected finding. Obesity in fact is notoriously associated with a lower risk of osteoporotic fracture [23]. The increase in FBM associated with a decrease in LBM and increased bone fragility could influence the occurrence of SRE being relevant to asthenia and patients predisposition to accidental falls.

It is indeed noteworthy that, in this study, changes in FBM seem to have a greater impact than changes in BMD in predicting bone fractures. This observation therefore needs confirmation.

The musculoskeletal side effects of ADT increase the risk for osteoporosis and fracture and can compromise the quality of life of PC patients. As a matter of fact, in a matched cohort study of more than 38,000 men in Ontario patients treated with ADT for PC experienced significantly more fractures of all types (17.2 vs. 12.7 %, $p = 0.0001$) and more fragility fractures (9.0 vs. 5.9 %, $p = 0.0001$) than matched patients not treated with ADT [24].

In this paper, neither changes in BMD nor changes in LBM were associated with an increased risk in SRE; in addition, none of these parameters were associated with patient TTP and OS. Again, the low potency of this study could account for the absence of correlation, particularly between BMD changes and SRE risk.

The present study has several limitations; (a) this is an unplanned post hoc analysis on a series of patients prospectively enrolled; (b) while this study is one of the first to prospectively examine the relationship of body composition with patient outcomes, it is unpowered to detect significant differences in patient outcome, so many of the non-significant findings may be due to low statistical power to detect these relationships rather than evidence of these variables not being predictive of the clinical outcomes assessed; (c) the study does not have a validation group; (d) part of the observed changes may have resulted from normal aging rather than ADT, although in a prospective study of healthy older men, FBM and LBM did not change significantly after 3 years [25]; (e) energy intake and physical exercise were not controlled and they could have influenced body composition outcomes.

These limitations notwithstanding the explorative data provided by this study are new and interesting. The potential implications are that diet and physical activity intervention adopted early to minimize the effects of ADT on FBM increase can have a positive impact on patient prognosis.

Conclusions

DXA scan is frequently used in PC patients under ADT with the aim to monitor BMD as a measure of risk on bone fracture. This study underlines the importance of assessing changes in FBM as a prognostic marker.

Healthy diet and physical exercise should be recommended in patients under ADT and should be started as early as possible to prevent metabolic syndrome and the risk of cardiovascular disease.

Monitoring in FBM during treatment can be a valid parameter to assess the efficacy of these preventive measures. Whether prevention of FBM increase can improve the ADT efficacy is an interesting issue that deserves to be addressed in a prospective randomized study.