HoSAGE: Sarcopenia in Older Patients before and after Treatment with Androgen Deprivation Therapy and Radiotherapy for Prostate Cancer

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HOSAGE: SARCOPENIA IN OLDER PATIENTS BEFORE AND AFTER TREATMENT WITH ANDROGEN DEPRIVATION THERAPY AND RADIOTHERAPY FOR PROSTATE CANCER

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Abstract: *Background:* Sarcopenia is a muscle disease defined by a loss of muscle strength associated to a decrease in skeletal muscle mass. In addition to aging, many factors may contribute to sarcopenia as cancer and/or androgen deprivation therapy (ADT). *Objectives:* The aims of this study are to describe the prevalence of sarcopenia in older prostate cancer patients before initiation of treatment with ADT and radiotherapy, and to evaluate the impact of ADT on the occurrence or aggravation of sarcopenia in this population. *Design:* longitudinal study. *Participants and setting:* Sarcopenia was prospectively evaluated in 31 consecutive patients aged 70 to 88 years, referred in one hospital unit of south eastern France, for a comprehensive geriatric assessment (CGA) before cancer treatment initiation. *Measurements and results:* CGA, measures of muscle strength and physical performances were performed at baseline (T0) and at the end of cancer treatment (T1). Appendicular skeletal muscle mass was measured by Dual-energy X-ray absorptiometry (DXA) at the end of treatment. At T0, 8 patients (among 31) had a probable sarcopenia according to European consensus, and 18 had altered physical performance. At T1, 15 patients (among 19) had abnormal one leg balance test. Finally, only one patient had a sarcopenia confirmed by DXA. *Conclusion:* This preliminary study showed a high prevalence of muscle disorders before initiation of ADT in a population of elderly cancer prostate patients with intermediate frailty status, and an increased risk of falls at the end of ADT. This highlighted the importance of screening for sarcopenia before treatment initiation, to prevent the occurrence or aggravation of sarcopenia by possible adjustment of treatment, and implementation of appropriate exercise and nutrition interventions.

Key words: Sarcopenia, older patients, prostate cancer, androgen deprivation therapy, radiotherapy.

Introduction

Prostate cancer is the most common cancer in old men (1). Six months to three years androgen deprivation therapy (ADT) is the reference treatment in localized, intermediate, and high-risk prostate cancer, associated with radiotherapy (2). ADT use has numerous side effects including alteration of physical functions and decrease of quality of life (3). Moreover, androgen inhibitors have been associated with metabolic effects that could lead to or worsen obesity, cardiovascular disease, sarcopenia or osteoporosis (4)

Sarcopenia is a muscle disorder characterized by loss of muscle strength and muscle mass with or without an increase of fat mass (5). In addition to aging, many factors may contribute to sarcopenia, as malnutrition, inactivity, or cancer disease. It is a risk factor of early death, falls and mobility impairment in older populations (5). Diagnosis is based on a combination of measures of muscle mass and muscle strength that vary according to the guidelines (table 1). Measures of physical performance are used to appreciate the severity of the disease.

New updated recommendations of the revised European guidelines (EWGSOP2) (5) aim to increase awareness of sarcopenia, promoting detection, prevention and treatment. In France, prevalence of sarcopenia in the elderly is poorly known and, until now, its detection in patients with ADT, is not part of national guidelines on prostate cancer management. In this particular context, our study aims to document (1) the prevalence of muscle disorders in older prostate cancer patients before initiation of ADT and radiotherapy, and (2) the occurrence and/or aggravation of muscle disorders and sarcopenia at the end of treatment.

Methods

This feasibility study was led between October ~~2018~~ and April 2019, in the Internal Medicine, Geriatric and Therapeutics Unit of the Marseille's University Hospital (AP-HM). During this period, all consecutive patients, aged 70 years or more, referred for a comprehensive geriatric assessment before initiation of radiotherapy and ADT for a localized or locally advanced prostate cancer, were enrolled in the study.

Data collection

Muscle mass was estimated at the end of cancer treatment with the Appendicular Skeletal Muscle Mass (ASMM)

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Table 1
Main diagnosis criteria of sarcopenia for men

Consensus	Measures	Cut-off points	Sarcopenia diagnosis
International working group on sarcopenia (6)	Physical function Skeletal muscle mass	Gait speed < 1m/s (over 4 m) DXA : ASSM/height2 ≤ 7,23 kg/m^2	Measure of physical function (Gait speed) and measure of lean mass (DXA)
European working group on sarcopenia in older people (EWGSOP2) (5)	Grip strength /chair stand test Skeletal muscle mass Performances	Grip strength < 27kg Chair stand test >15s for 5 rises DXA: ASSM/height^2 <7.0kg/m^2 Gait speed ≤ 0.8m/s SPPB Score ≤ 8 points TUG ≥ 20s 400-meter walk completed in ≥ 6min or not completed	Reduced muscle strength : probable sarcopenia Reduced muscle mass : confirmed sarcopenia Reduced performances: severe sarcopenia
Asian Working Group for Sarcopenia [7]	Strength Performance Skeletal muscle mass	Grip strength < 26kg Gait speed < 0.8 m/s (over 6 m) DXA : ASSM/height^2 < 7,0 kg/m^2 BIA < 7.0 kg/m^2	Low lean mass (DXA) and reduced muscle function (Grip strength and Gait speed)

SPPB : Short Physical Performance Battery; TUG : Timed Up and Go; ASSM: Appendicular Skeletal Muscle Mass; BIA: Bioelectrical Impedance Analysis; DXA: Dual-energy X-ray absorptiometry; The skeletal muscle mass can also be estimated by bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI) or computed tomography (CT) in research studies.

measured with dual-energy X-ray absorptiometry (DXA). Results were adjusted for body size using height squared (ASMM/height^2) and chosen cut-off point for low muscle quantity was <7.0 kg/m^2 (5).

All other information was collected twice, before initiation and at the end of cancer treatment. Muscle strength was measured using hand grip strength test (GS) that was conducted using the methodology of the American Society of Hand Therapists (ASHT) (8) and the cut-off points recommended in the EWGSOP2 (5). To determine severity of sarcopenia, physical performances were measured with gait speed (9), and "Timed up and go test" (10) (TUG). Geriatric frailties were detected using G8 screening tool (11), vulnerability score (ECOG-PS (12)), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) tools (13, 14). Fall risk was assessed using One Leg Balance test (OLBT) (15) and history of falls. Nutritional status was evaluated using Body Mass Index (BMI), Albumin level, Mini Nutritional Assessment scale (MNA) (16) and protein intake. Definition of malnutrition was issued of French Health Ministry recommendations (BMI <21 and/or Albumin level<35g/l and/or MNA<17) (17). The Mini Mental State Examination (MMSE) (18) and the Clock Drawing (CD) test were used to detect cognitive disorders (MMSE<24 and/or CD test <6). Patients were asked about their socio-demographic characteristics and their life habits (physical activity, alcohol and tobacco consumptions). People living alone and/or with no family caregiver within 50 kilometers were considered as socially isolated. Finally, cancer clinical characteristics and treatment, poly-medication (≥ 5 drugs), and comorbidities were issued of medical records. All data were collected by the same physician. This study was approved by the Ethics Committee.

Statistical analysis

Chi square test and t-test were used to perform comparative analysis of discrete and continuous variable respectively. McNemar and Wilcoxon tests were respectively used to analyze paired discrete and continuous data. All analyses were done using SPSS for Windows, version 17.0.

Results

Prevalence of sarcopenia and muscle disorders before treatment initiation

Baseline characteristics of the 31 patients enrolled are detailed in table 2. Mean age was 80.4 years, most were highly educated (n=19) and a majority had an income greater than two times the minimum old-age pension (n=16). Half (n=14) had a high-risk prostate cancer, eight were dependent for IADL, and only eleven reported regular physical activity. According to the revised European consensus, eight patients (25%) had a probable sarcopenia at baseline. Moreover 18 patients had altered physical performance with TUG ≥ 20s for eight of them, OLBT <5s for thirteen and gait speed ≤ 0.8m/s for eleven. Compared with patients without sarcopenia, those with probable sarcopenia had more geriatric frailties, higher fall risk, more medications, and more often high-risk cancer, although the differences did not reach significance (table 2).

Prevalence of sarcopenia and muscle disorders at the end of treatment

Nineteen patients received ADT and radiotherapy, and had a follow-up visit at the end of treatment. Radiotherapy delivered was on average 75.6 Gy. Eight patients received ADT for 6 months, ten for 15 months, and the last one for 18 months. Among the thirteen patients with no sarcopenia at baseline, six

Table 2

Sociodemographic, oncologic and geriatric characteristics according to sarcopenia status before initiation of oncologic treatment (n=31 old men with prostate cancer)

Characteristics	Total population		No sarcopenia (hand grip ≥27kg) N=23		Probable sarcopenia (hand grip <27kg) N=8		
	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	p
Socio-demographic characteristics							
Age	80.5±4.3	[70-88]	80.4±4.1	[73-88]	80.6±4.9	[70-86]	0.555
High school graduation or more	20	66.4	13	(56.5)	6	(75.0)	0.215
Living < 50km from treatment center	26	83.9	18	(78.3)	8	(100.0)	0.291
Caregiver present	27	87.1	20	(86.9)	7	(87.5)	1.000
Income (≥2000)	16	51.6	11	(47.8)	5	(62.5)	0.399
Social isolation *	4	12.9	3	(13.0)	1	(12.5)	1.000
Oncologic characteristics							
Intermediate-risk prostate cancer	14	45.2	13	(56.5)	1	(12.5)	0.077
High-risk prostate cancer	14	45.2	8	(34.8)	6	(75.0)	
Unknown	3	9.6	2	(8.7)	1	(12.5)	
Geriatric characteristics							
G8 score (≤14)	16	51.6	11	(47.8)	5	(62.5)	0.399
Dependence ADL <6	1	3.3	0	(0.0)	1	(12.5)	NA
IADL <4	8	77.4	5	(21.7)	3	(37.5)	0.393
Nutrition BMI	26.6±3.6	[21-42]	27.0±4.0	[22-42]	25.6±2.3	[21-28]	0.682
Albumin	41.8±2.5	[37.6-47.9]	41.8±2.3	[37.6-47.0]	41.8±3.1	[38.0-47.9]	0.954
Protein intake** (g)	80.4±20.6	[21-110]	85.5±14.2	[52-110]	70.2±27.9	[21-108]	0.186
Malnutrition ***	3	9.6	2	(8.7)	1	(12.5)	1.000
Cognitive troubles	4	12.9	2	(8.7)	2	(25.0)	0.268
Depressive syndrome	5	16.1	2	(8.7)	3	(37.5)	0.093
Mobility TUG (≥20s)	8	25.8	6	(26.0)	2	(25.0)	1.000
Gait speed (≤0.8m/s)	10	32.3	7	(30.4)	3	(37.5)	0.697
Fall risk One leg balance test (<5s)	13	41.9	9	(39.1)	4	(50.0)	0.689
Fall history (past 3 months)	4	12.9	3	(13.0)	1	(12.5)	1.000
Number of comorbidities	3.4±1.6	[0-7]	3.2±1.6	[0-7]	3.9±1.6	[2-6]	0.411
Polypharmacy (≥5 drugs)	18	58.1	12	(52.2)	6	(75.0)	0.412
Alcohol consumption ****	20	64.5	17	(56.7)	3	(10.0.)	0.181
Smoker or former smoker	15	48.4	14	(46.7)	1	(3.3)	0.080
Physical activity							
Less than 30 min a week	10	32.3	8	(34.8)	2	(25.0)	0.589
30 min once or twice a week	10	32.3	6	(26.1)	4	(50.0)	
30 min 3 times or more per week	11	35.5	9	(39.1)	2	(25.0)	

* Social isolation : patient living alone with caregiver living over 50km away or without caregiver; ** Mean protein intake over 3 days in grams; *** Definition of the French High Health Authority (HAS): BMI <21 and/or Albumin <35g/L and/or MNA <17; **** At least one glass of wine by day

had a muscle strength decrease. No relation was found between muscle strength decrease and ADT duration. After ending treatment, fifteen patients had abnormal OLBT, suggesting a significant increase of fall risk.

Out of the 19 patients with a follow-up, six agreed to have their muscle mass measured with DXA. ASSM/height2 was lower than 7.0 kg/m² for two patients but only one had a sarcopenia according to the EWGSOP2 guidelines.

Discussion

In this study among 31 older patients with prostate cancer, the estimated prevalence of probable sarcopenia before cancer treatment was 25% according to the last European consensus. The first follow-up showed an increased risk of falling at the end of treatment.

Prevalence rate of sarcopenia varies between studies

Table 3
Comparison of sarcopenia status, social and geriatric characteristics before and after prostate cancer treatment (N=19)

Characteristics	T0		T1		p
	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	
Handgrip Strength	30.6±8.7	[16-51]	30.6±7.9	[20-50]	0.875
Normal	13	(68.4)	13	(68.4)	1.000
Probable sarcopenia (<27kg)	6	(31.6)	6		
Social isolation					
No	15	(78.9)	17	(89.5)	0.500
Yes	4	(21.1)	2	(10.5)	
Polymedication					
<5 drugs	8	(42.1)	7	(36.8)	1.000
≥5 drugs	11	(57.9)	12	(63.2)	
Cognitive status					
Normal	19	(100)	15	(78.9)	NA°
Cognitive troubles	-	-	4	(21.1)	
Nutritional status					
BMI	26.1±2.6	[21-32]	25.5±3.2	[18-31.9]	0.177
Albumin	41.7±2.6	[37.6-47.9]	41.6±2.9	[37.3-48.4]	0.798
Protein intake*	75.7±22.5	[21-110]	79.6±21.5	[36-114]	0.445
Normal nutritional status	17	(89.5)	17	(89.5)	1.000
Malnutrition**	2	(10.5)	2	(10.5)	
Activities of Daily Living score					
6	18	(100)	17	(94.4)	NA°
<6 (Dependent)	-	-	1	(5.6)	
Instrumental Activities of Daily Living score					
4	16	(88.9)	11	(61.1)	0.125
<4 (Dependent)	2	(11.1)	7	(38.9)	
Mobility					
Physical activity					
Less than 30 min a week	8	(42.1)	8	(42.1)	1.000
More than 30 min a week	11	(57.9)	11	(57.9)	
Timed up and go Test (TUG)					
< 20s	15	(78.9)	9	(47.4)	0.070
≥ 20s	4	(21.1)	10	(52.6)	
One leg balance test (OLBT)					
≥ 5s	10	(52.6)	4	(21.1)	0.031
< 5 s	9	(47.4)	15	(78.9)	
Gait speed					
> 0,8m/s	12	(66.7)	12	(66.7)	1.000
≤0.8m/s	6	(33.3)	6	(33.3)	

* Mean protein intake over 3 day in grams; ** Definition of the French High Health Authority (HAS): BMI <21 and/or Albumin <35g/L and/or MNA <17; ° McNemar test application criteria were not met; T0 : before cancer treatment; T1: at the end of cancer treatment

according to the population studied and the criteria used for diagnosis. Estimation of probable sarcopenia prevalence varies across studies from 1.6% in healthy elderly (19) to 40% in community-dwelling Brazilian old men (20). Using the EWGSOP definition, prevalence of confirmed sarcopenia in community-dwelling populations, varies from 1 to 29% (21). Risk factors as age, cancer, malnutrition, or frailty have been involved in the development of sarcopenia (22,

23). Different studies have also shown a relation between sarcopenia and institutionalization of individuals (19) or low socio-economic status (20). Our study population consisted of community-dwelling older adults, highly educated and well-off, with good nutritional status, intermediate frailty status according to Fried criteria (24), and localized prostatic cancers with a favorable prognosis (1). Considering their health and social characteristics, they had a lower risk of sarcopenia than the populations usually described in the literature, especially those with cancer (22). The observed prevalence of probable sarcopenia was therefore higher than expected.

At the end of treatment, 80% of our studied population had an abnormal OLBT, suggesting a fall risk increase. This is consistent with results of others who reported incidence rates of falls in prostate cancer patients treated with ADT, up to twice as high than in those without ADT (25, 26). Among ADT side effects, several studies reported lean mass loss, and muscle strength decrease (27, 28), both related to ADT duration. Unlike others, we did not show any muscle loss or decrease in muscle strength in patients treated with ADT, probably because of the size of our study sample (19 follow-up until now and 6 patients who agreed to have their muscle mass measured). The small number of patients, and the lack of post treatment evaluation for part of them (ongoing treatment) are the major limitations of this preliminary study. However, thanks to first results, a hundred more patients will be enrolled (with a control group of prostate cancer patients receiving only radiotherapy) and followed for one year after the end of treatment.

Our study showed a high prevalence of muscle disorders among elderly considered at low risk of sarcopenia. This result stresses the importance of systematically screening for sarcopenia before initiating ADT, to reduce ADT adverse effects with adapted nutritional and exercise interventions (4, 29). Current guidelines for older adults with prostate cancer recommend to associate radiotherapy with 6 to 36 months of ADT. The close link between sarcopenia and frailty, and their negative impact on survival are well known. More studies are needed to improve knowledge about the risks of occurrence or aggravation of a sarcopenia during ADT, to help physicians to determine the modalities of treatment (as intermittent ADT (4) or shorter treatment (30)) offering patients the most satisfactory benefit-risk ratio.

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