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ORIGINAL ARTICLE

The ADAPP trial: a two-year longitudinal multidisciplinary intervention study for prostate cancer frail patients on androgen deprivation associated to curative radiotherapy

Julie Mareschal[a]*, Kerstin Weber[b]*, Pascale Rigoli[a], Edmund Biason[c], Laura Frambati[b], Carole Gotteland[d], Thomas Zilli[d], Claude Pichard[a] and Raymond Miralbell[d]

[a]Clinical Nutrition, Department of Internal Medicine Specialities, Geneva University Hospital, Geneva, Switzerland; [b]Liaison Psychiatry and Crisis Intervention, Department of Mental Health and Psychiatry, Geneva University Hospital, Geneva, Switzerland; [c]Physical Medicine and Orthopaedics Rehabilitation, Department of Surgery, Geneva University Hospital, Geneva, Switzerland; [d]Radiation Oncology, Department of Oncology, Geneva University Hospital, Geneva, Switzerland

ABSTRACT

Background: Androgen deprivation (AD) therapy combined to radiotherapy (RT) is a curative therapeutic option for patients with non-metastatic locally advanced or aggressive intermediate prostate cancer (PC), though with a range of nutritional, physical, and psychological side effects. A multidisciplinary care program was created to help frail patients to prevent and manage those side effects.

Material and methods: We conducted a longitudinal interventional study in frail patients, presenting either cardiovascular/pulmonary comorbidities, old age (≥75 years), vulnerability ratings, or balance impairment. Patients were treated by AD and RT and, benefited from nutritional coaching, supervised biweekly 45 minute physical training, and psychological counseling for two years. Treatment outcomes included PC-related quality of life (QoL), body mass index, fat mass index, and fat-free mass index derived from bioelectrical impedance analysis, Six-Minute Walk Test, Timed Up&Go, handgrip strength, Hospital Anxiety and Depression scale, Mini Mental State Examination. Measures were repeated after zero, three, six, nine, 12, 18, 24 months, and 12-months post-study follow-up. A prospective mixed-model design was used to assess longitudinal outcome.

Results: Regression analyses revealed no significant change over the two years, including post-study follow-up. Means of QoL, nutritional, physical, as well as psychological variables remained stable over more than two years in the 35 men aged 74 (range 68–76) years.

Conclusion: The expected side effects of AD and RT were not observed in frail PC patients who followed this multidisciplinary care program.

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In developed countries, prostate cancer (PC) is the most frequent malignancy among men (i.e. 23.0% of all new cases per year) [1]. External beam radiotherapy (EBRT), often combined to androgen deprivation (AD) therapy, is a curative treatment option for patients with localized or locally advanced PC. The results of several phase III trials strongly support the beneficial role of AD when combined with EBRT as metastasis-free [2].

Unfortunately, the therapeutic benefit of AD is negatively balanced with the possible onset of side effects related to an increase in fat tissue, to loss of muscle mass, as well as to metabolic, sexual, and/or mood cognitive disorders. Such side effects may significantly worsen the physical and psychological condition of patients, and negatively influence their quality of life (QoL), especially those who are frail [3].

Well established ways of measuring frailty in old age have been developed such as Fried et al. who define frailty as a vulnerable health condition resulting in a decreased ability to respond to a stressor [4]. More precisely, frail older adults present three of five following criteria: weight loss, exhaustion, weakness, slowness, and low physical activity level. The term 'prefrail' is defined as the presence of one or two of these criteria. Hurria et al. suggests a cancer-specific definition of frailty in old age designating adults who are at higher risk for cancer treatment toxicity because of age-associated conditions such as functional losses, cognitive impairment, or physiologic changes [5]. All these symptoms have been associated with AD in locally advanced cancer patients [6].

Therefore, the management of AD's side effects is the utmost challenge for prefrail and frail locally advanced PC patients. We hypothesize that a multidisciplinary accompaniment (including nutritional, physical, and psychological coaching) for PC frail patients on AD associated to curative RT would stabilize QoL by preventing and/or improving the further debilitating side effects of AD. However, to our knowledge, no studies have evaluated the impact of such multidisciplinary approach in these patients. Therefore, in 2010, we launched a longitudinal multidisciplinary intervention

CONTACT Julie Mareschal julie.mareschal@hcuge.ch Clinical Nutrition Unit, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
*These authors contributed equally to this work.

program the 'accompaniment protocol for frail PC patients on AD and EBRT' or 'Accompagnement lors de Déprivation Androgénique des Patients Prostate' (ADAPP), in French. This study aims at evaluating during the two years of follow-up: (1) the QoL, and (2) the body composition, the physical function, and the psychological status of patients.

Material and methods

This longitudinal interventional study was performed between March 2010 and January 2014. Thirty-five patients from the Division of Radiation Oncology at the Geneva University Hospital were recruited. Adopting a geriatric oncology approach of frailty, eligible PC patients with non-metastatic locally advanced or aggressive intermediate disease were treated with AD and EBRT, and were: (1) old (age $\geq$75 years, 48%) and/or presenting with at least one out of the following functional or physiological frailty criteria, (2) cardiovascular/pulmonary comorbidities with Charlson Comorbidity Index (CCI) $\geq$ 3 (93%), (3) Vulnerable Elders Survey-13 $\geq$ 3 (31%), or (4) balance unipedal stance test $<$5 seconds (28%).

Exclusion criteria were expected survival $<$16 weeks and incapacity for discernment and collaboration based on the judgment of the radiation oncologist expert in PC.

All patients received AD therapy before, during and after EBRT. They started by taking an antiandrogen for 30 days, bicalutamide (Casodex®), 50 mg daily, followed two weeks after by three-monthly injections of a luteinizing hormone releasing hormone (LH-RH) agonist (Eligard®, Lucrin®).

An attending radiation oncologist expert in PC, a nurse trained in the management of PC patients, a dietician, a physiotherapist, and a psychologist were the members of the accompaniment team. The nurse and the radiation oncologists were charged to recruit, inform, and follow the patients during the treatment interval as well as to coordinate and organize the appointments with the other team members.

Enrolled patients had nutritional coaching in addition to supervised group physical training and psychological counseling. The dietician monitored body composition and prevention of unwanted weight increase every three months. The physiotherapist was in charge of keeping the balance of the lean body mass and fighting the fatigue with 45 minutes combined aerobic and resistance exercises twice a week in a supervised group setting. The psychologist offered psychological counseling and emotional support by individual or in couple sessions adapted to each patient's personal situation and needs.

Trained professionals in each field assessed QoL treatment outcomes, nutritional, physical and, psychological status. Patients were evaluated at the start of AD and three, six, nine, 12, 18, and 24 months or at discharge, thereafter. Patients were discharged from the study at the time that total testosterone blood levels turned back to normal or two years maximum after stopping AD. A last follow-up was planned 12 months after study discharge.

QoL was evaluated with a standardized questionnaire of Clark et al., assessing PC-related QoL [7]. This multi-item questionnaire rated on Likert scales measures seven sub-domains including behavioral consequences of urinary dysfunction, sexual intimacy, sexual confidence, marital affection, masculine self-esteem, health worry, and PSA concern. In addition, four sub-domains assess patients' perception of the treatment process and its effectiveness: informed decision, decision regret, cancer control, and outlook on life (coping with cancer). Higher scores (range 0–100) indicate higher levels of QoL, except for prostate-specific antigen (PSA) concern, health worry, and regret.

Body composition was assessed using body mass index (BMI), fat-free mass index (FFMI), and fat mass index (FMI). BMI is defined as weight (kg) divided by height (m) squared. FFMI and FMI are derived from bioelectrical impedance analyzer (BIA) (Nutriguard M; DataInput GmbH, Darmstadt, Germany) [8]. A measured resistance and reactance were obtained and allowed the calculation of fat-free mass (FFM) by using the Geneva BIA formula validated against dual-energy X-ray absorptiometry in 343 healthy white subject with a BMI between 17.0 and 33.8 kg/m^2, and aged 22–94 years [9]. Fat mass (FM) was obtained by subtracting FFM from body weight. FFMI and FMI were defined as FFM and FM, respectively, divided by the height (m) squared.

Physical function was measured using validated physical performance tests: the Six-Minute Walk Test (6MWT), the Timed Up&Go (TUG), and the handgrip strength (HGS). The 6MWT is a submaximal aerobic test that evaluates walking endurance. It measures, in meters, the distance that an individual can quickly walk along a 50-m unobstructed indoor corridor in a period of six minutes [10]. Patients additionally self-rated their perceived exertion using the Borg scale, varying from 6 to 20. A perceived exertion of 12 would be expected. The TUG is a functional test that assesses mobility and balance [11]. It evaluates the time, in seconds, that a person takes to stand from a chair, walk 3 m, then turn around, walk back to the chair and sit down again. The last test, HGS, measures the upper extremity strength in kilograms with a handheld dynamometer (Jamar® Hydraulic Hand Dynamometer, Patterson Medical, Warrenville, Canada) set in handle position 2. It is a predictor of overall muscle strength and functional capacity [12]. Three measurements on each hand were recorded. A mean for each hand was calculated.

The psychological status was evaluated using the Mini Mental State Examination (MMSE) and Hospital Anxiety and Depression scale (HAD-A&D). The MMSE is a 30-point questionnaire that measures cognitive impairment [13]. A score $<$24 was considered as pathologic threshold, independently of patient's age and educational level. The HAD-A&D scale was developed to detect states of anxiety and depression in general hospital practice [14]. Scores $>$8 (range 0–21) indicate clinically relevant states, needing further investigation.

Baseline characteristics for all patients were summarized with descriptive statistics for continuous and categorical variables. Primary and secondary outcomes were treated as continuous measures and analyzed with linear mixed effects regression models that take in account repeated and potentially correlated measurements within each subject. This allows the inclusion of subjects with only partial longitudinal

follow-up data. Measurements subjective QoL, body composition, physical, as well as psychological functioning at all follow-up time-points were the dependent variables. Covariates included age, AD, and EBRT duration, as well as duration of multidisciplinary care. A p value of 0.05 was used. Statistical analyses were performed using Stata (version 14; College Station, TX, USA).

The Ethical Committee of the Geneva University Hospital exempted the investigators of the need to obtain a formed signed consent from the patients as ADAPP program was part of a quality of care program supported by our institution. The study was carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki. The study was explained to patients by the investigators and an information document. Patients could refuse to participate.

Results

Almost all potentially eligible patients accepted to participate in the program. Baseline sample characteristics are displayed in Table 1. EBRT was started 3–8 months after the initiation of AD. Reasons for exiting the program before the target of two years after the end of AD were recovery of initial testosterone level (29%), metastatic cancer (9%), drop-out (11%), or other (14%, such as death or relocation). In summary, 23% of the patients were followed for at least 12 months, 20% for 18 months, and 37% were followed for ≥24 months.

As summarized in Table 2, regarding subjective QoL at baseline, compared to the reference group reported by Clark et al. [7] defined as a group of patients randomly sampled with a normal PSA test result (<4.0 ng/ml) in the last 12 months, and no recorded history of PC, the present sample was scored with a lower QoL due to problems such as living with urinary dysfunction, sexual intimacy, and masculine self-esteem, as well as enhanced PSA concern. Patients reported, no impact on sexual confidence, on marital affection, and presented less health worries and apprehensiveness than the reference group. Furthermore, compared to the reference group, patient's perception of the treatment process and its effectiveness showed a low feeling of cancer control (e.g. fear of recurrence or progression), and a low treatment compliance. Finally, they reported few decision regrets. Indeed, patients explained that they had to cope with excessively detailed information. They had all the information needed, but felt overwhelmed by the complexity of the cancer treatment and multidisciplinary accompaniment. Actually, they reported that coping with cancer has made them stronger which resulted in a better outlook on life.

At study entry, patients were considered to be obese with excessive FM in accordance with FMI. FFMI was within the standard range [15]. Regarding physical condition, walking endurance capacity (6MWT) was also within the healthy range. Patients rated the test as 'somewhat hard' on the Borg scale. The level of mobility and balance (TUG) was located just below the 10 second threshold, and the muscle strength (HGS) ranked within the population mean. Psychological assessment revealed absence of cognitive impairment, as well as absence of clinically significant anxiety or depression

Patients' subjective experience as self-reported on the PC-related QoL scale showed no deterioration over time [$n = 152$ measures, 29 patients, median 5 (range 1–9) measures/patient] for urinary dysfunction ($p = 0.071$), sexual intimacy ($p = 0.134$), sexual confidence ($p = 0.498$), masculine self-esteem ($p = 0.342$), and marital affection ($p = 0.065$). PSA concern did not increase ($p = 0.277$) and health worries even significantly decreased from 20.8 to 15.8 between baseline and discharge, and continued to decrease at last follow-up to 14.4 ($p = 0.028$).

Regarding patients' perception of the effectiveness of their treatment, mixed effects regression models analyzing change

Table 1. Baseline characteristics.

Characteristics	Prostate cancer patients ($n = 35$)
Frailty	
Age (year)	74 (68–76)
Charlson Comorbidity Index	5 (4–5)
Vulnerable Elders Survey	2 (1–3)
Unipedal Stance Test <5 s	10 (28.6%)
Disease severity	
Stage	
cT1c	3 (8.5%)
cT2	10 (28.6%)
cT3	22 (62.9%)
Gleason score	7 (7–9)
PSA level (ug/l)	10.7 (6.5–27.0)
Testosterone (ug/l)	2.8 (2.1–3.9)
Treatment duration	
Androgen deprivation (months)	6 (3–9)
Radiotherapy (weeks)	7 (5–8)
Multidisciplinary care program (months)	24 (15–30)

Data are median (min-max) or number (%).

Table 2. Baseline health status and quality of life.

Characteristics	Prostate cancer patients ($n = 35$) Mean (SD)	
Nutritional parameters		
Body mass index (kg/m^2)	30.2 (3.5)	
Fat mass index (kg/m^2)	9.9 (2.1)	
Fat-free mass index (kg/m^2)	20.6 (1.7)	
Physical parameters		
Handgrip strength (kg)	38.4 (8.8)	
Six-minute walk test (m)	486.8 (115.5)	
Borg scale (6–20)	11.4 (2.1)	
Timed Up&Go (second)	9.1 (2.9)	
Psychological parameters		
Cognition (0–30)	27.4 (1.7)	
Anxiety (0–21)	6.4 (2.9)	
Depression (0–21)	4.7 (3.8)	
Quality of life (0–100)		Reference group[b]
Urinary dysfunction	86.5 (16.1)	91.0
Sexual intimacy	62.8 (28.4)	70.0
Sexual confidence	64.7 (23.2)	45.8
Masculine self-esteem	73.7 (18.6)	85.2
Marital affection	92.9 (13.8)	79.6
Health worry[a]	20.8 (12.9)	26.5
PSA concern[a]	55.1(27.9)	39.6
Treatment effectiveness (0–100)		
Cancer control	62.7 (16.1)	68.1
Informed decision	34.1 (19.4)	72.7
Decision regret[a]	10.0 (13.3)	15.8
Future outlook	64.2 (25.9)	47.4

[a]Higher scores indicate negative perception;
[b]See [14].

from baseline to 12-month post-study follow-up revealed that, their treatment compliance remained stable ($p = 0.482$) with no increase of decision regrets ($p = 0.936$) after adjusting for confounding variables. Their feeling of being in control of the cancer significantly increased [$p = 0.046$, $n = 124$ measures, 29 patients, median 4 (range 1–7) measures/patient] throughout the multidisciplinary care program (from 62.7 to 71.00), without losing in intensity at follow-up 12 months later (72.7), independently of patients' age and AD, EBRT, or ADAPP treatment durations. In parallel, their feeling of coping with the cancer and outlook for the future significantly decreased over time ($p = 0.002$), dropping from 64.2 to 50.0 at discharge and even 36.3 at 12-month follow-up, and thus approaching the level of a PC reference group. This later change was significantly related to the duration of AD: the longer the AD therapy, the lower the future outlook and feeling of coping ($p = 0.012$).

Regarding body composition, no statistically significant decline over time neither for the BMI ($p = 0.315$), the FMI ($p = 0.277$) and the FFMI ($p = 0.412$) [$n = 168$ measures, 32 patients, median 5 (range 1–7) measures/patient] were revealed. The three nutritional parameters remained stable over time, after adjusting for duration of age, AD, EBRT, and multidisciplinary care program.

Likewise, regarding physical function, all four variables remained stable over more than two years, after adjustment for covariates [$n = 129$ measures, 31 patients, median 4 (range 1–7) measures/patient]. Handgrip strength remained within the health population mean (HGS, $p = 0.055$), as well as walking endurance (6MWT, $p = 0.116$), Borg scale ($p = 0.212$), and patients' level of mobility and balance (TUG), which remained below the 10 seconds threshold throughout the study ($p = 0.416$).

Regarding psychological performance, patients' level of cognitive functioning showed no significant decline [MMSE, $p = 0.270$, $n = 167$ measures, 32 patients, median 5 (range 1–9) measures/patient]. The level of anxious and depressive mood remained below the clinically significant threshold throughout the longitudinal assessments [HAD-A $p = 0.466$, HAD-D $p = 0.924$, $n = 125$ measures, 29 patients, median 4 (range 1–7) measures/patient], after adjusting for age and treatment durations.

Discussion

This multidisciplinary care program was beneficial for non-metastatic locally advanced or aggressive intermediate PC frail (and prefrail) patients receiving AD combined with EBBRT by preventing and managing the side effects of AD. Confirming our hypothesis, QoL, nutritional, physical, and psychological variables showed no significant change and remained stable during the entire study and even at follow-up.

It has been previously reported that body composition, physical function, sexual function, mental and emotional wellbeing, and QoL were diminished during AD therapy for PC [3]. Most interventional studies published so far have assessed the impact of physical exercise alone on the above-mentioned side effects with results similar to ours. Recently, Cormie et al., have revealed that a three-month supervised twice-a-week aerobic and resistance exercise program was beneficial for non-metastatic PC patients on AD [16]. Moreover, this preventive approach succeeded to preserve the patient's lean mass, to prevent FM gain, to maintain walking endurance with 6MWT, and to improve sexual function and QoL. Another study has evaluated the effects of 16-week aerobic and resistance exercise program, including home-based and weekly group sessions, for men receiving AD [17]. Again, the exercise program attenuated the side effects of AD by maintaining BMI, 6MWT, and QoL. According to Segal et al., a 24-week both resistance and aerobic exercise program reduced fatigue. Resistance exercise alone also improved QoL, lower body strength, triglycerides, and body fat [18]. However, in this study only 61% of PC patients receiving radiation therapy benefited from AD. Physical activity may also improve physical function and lean body mass but without effects on FM but this last study is not comparable to ours [19]. The physical training program consisted of 16-week of whole body resistance exercise, three days per week and was not associated to aerobic exercise.

Several authors have investigated the combined effects of supervised physical activity and nutrition counseling. O'Neill et al., recruited PC patients deemed to receive at least six months of AD [20]. A six-month home-based aerobic exercise and dietary plan intervention reduced BMI and FM, improved aerobic endurance (6MWT), and preserved FFM and QoL. In another study including patients on long-term AD, BMI remained stable whereas aerobic exercise tolerance and QoL increased after 12 weeks of aerobic and resistance exercise and dietary advice [21]. This study is among the few evaluating the outcome six months after the end of physical and nutritional support. Unfortunately, the improvements in QoL after the 12-weeks intervention were not maintained.

As far as psychological counseling is concerned, previous studies on the benefits of psychosocial interventions for PC patients have revealed only slight and short-term beneficial effects in some domains of wellbeing, such as physical components of QoL and cancer-related QoL when compared with non-proactive ordinary care [22]. Symptom-related QoL, psychological distress or depression have not improved significantly. A recent review by Mazzarello et al., recommended focusing on the assessment of all stages of treatment with an active monitoring of patients' evolution, as well as the use of PC-specific QoL measures, as it was done in our program intervention [23]. Indeed, our results showed that over a time frame of more than two years, patients' subjective cancer-related QoL remained stable for several domains such as sexual intimacy and confidence, masculine self-esteem, and marital affection. Mazzarello et al. also recommended assessing anxiety, coping skills, and self-efficacy in addition to the more traditional depression outcome [23].

Results of the present study confirm the importance of choosing appropriate outcome measures, focusing not merely on psychiatric symptoms such as depression, but assessing, in addition, patients' individual coping and adjustment skills. In the ADAPP program, PSA checks did not increase patients' concern and health worries even significantly decreased between baseline and discharge. Our data

reveal how informed consent and the feeling of being in control of cancer management significantly increased among patients in the ADAPP study throughout the program and even beyond, regardless of age or AD duration. Their perspectives on the disease, treatment expectations, and their personal coping capacities became more and more realistic without any loss of subjective wellbeing or increase in depressive and anxious mood.

Furthermore, previous recommendations have stressed the need to integrate psychosocial care within multidisciplinary care programs for cancer patients [24]. Results of the present study suggest the benefits of offering systematically psychological counseling integrated in a multidisciplinary management program. The absence of cognitive decline and prevention of clinically significant depression and anxiety symptoms among ADAPP patients, unlike studies focusing on isolated psychosocial interventions, may suggest a superior effect of psychological interventions when these are integrated together with physical and nutritional counseling.

Another important point is that physical exercise in group settings appears to be essential. Positive feedback from our patients suggested that group emulation helps to manage physical and psychosocial side effects of AD. The group training sessions allowed patients exchange about the experience of their cancer and its treatment. Moreover, supervised group training sessions have been shown to promote patients' adherence and compliance [25]. This is in agreement with our findings. The majority of patients in the group training sessions were motivated, and the rate of absenteeism was low.

The main strengths of our trial are the multidisciplinary care program applied for frail patients and the long-time follow-up. Enrolled patients benefited from nutritional coaching in addition to physical training and psychological counseling. Patients were followed for two years with several time milestones: zero, three, six, nine, 12, 18, and 24 months followed by a last control 12 months after the 24th month milestone. For most studies on PC including patients receiving AD, the durations of the intervention period were shorter. Furthermore, few studies have evaluated outcomes following withdrawal of intervention. It is not possible to determine whether these observed benefits would persist over longer intervention duration and post-study follow-up. The only study which assessed outcomes six-month post-study follow-up concluded that improvements after intervention were not maintained [21]. Probably too short intervention would not help to maintain the benefits obtained through the intervention. Moreover, all those trials were not conducted by a multidisciplinary team including a dietician, a physiotherapist, a psychologist, an attending radiation oncologist, and a nurse coordinating the coaching actions. Benefits of a multidisciplinary care program are numerous for patients and healthcare providers [26]. Indeed, every frail patient is referred for opinion to all caregivers in order to establish an individually tailored management strategy while developing an optimal team interaction between all medical and paramedical actors.

Nonetheless, several pitfalls in the study have to be underscored. First, the study did not include a control, non-interventional group. Several previous randomized trials showing that a close coaching by the dietician, the physiotherapist, or the psychologist has positive effects in PC patients on AD compared to controls groups [16,17,20,21]. In this study, however, it was decided to offer the intervention to all frail and prefrail patients. Each patient was his own control. Second, an additional bias was the fact that subjects were all motivated volunteers. The ADAPP program required a significant engagement in terms of time with regular assessments not easy to adhere to. In routine care, it is likely that PC patients may not easily accept to follow a coaching program as complex and intensive as the one proposed by ADAPP. Last but not least, questions arise about the indication to offer to frail patients a curative treatment combining AD and EBRT over a simple watchful waiting strategy. Although in older and frail patients the risk of dying from other causes other than PC is probably higher than in younger and healthy men [27], a curative approach using modern RT techniques combined with a short-course AD (median six months) as proposed in the ADAPP trial may be justified to avoid morbidity related to local progression and spare patients from side effects of a long-life AD use in case of metastatic progression. Moreover, as confirmed by long-term results of the Scandinavian Prostate Cancer Group-7 phase III randomized trial and despite the baseline comorbidities, it is not excluded that in these patients a survival benefit may also be expected by adding prostate RT to lifelong AD [28].

The expected side effects of AD combined with EBRT were not observed in frail non-metastatic locally advanced or aggressive intermediate PC patients who followed a two-year nutritional, physical, and psychological multidisciplinary care program. However, further research is warranted to replicate the results of the present study in a large clinical sample in comparison to a control group receiving no preventing care for treatment side effects.

Disclosure statement

No potential conflict of interest was reported by the authors.

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