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## THERAPEUTIC APPROACHES

## Treatment of prostate cancer in unfit senior adult patients

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## SUMMARY

Prostate cancer is a disease typical of the elderly with a peak of incidence at 80 years.

As most patients aged  $\geq 70$  years show impairment of physical and/or cognitive performance, a complete geriatric assessment should be mandatory before planning any oncological treatment, in order to remove treatable conditions and to estimate the individual cancer-independent survival probability.

In unfit patients with early prostate cancer watchful waiting represent the best strategy when the chance of living  $< 10$  years and the benefit from any upfront active treatment would be poor. Radiotherapy should be sometimes offered to vulnerable patients having high risk prostate cancer.

Even in locally advanced prostate cancer active treatment could be deferred in asymptomatic patients, with short individual cancer-independent survival and well or moderately differentiated tumour.

When hormonal deprivation therapy is administered a great attention should be paid to potential adverse events, that could precipitate the physical performance and accelerate the development of severe frailty.

In the metastatic setting, the best supportive care, including bisphosphonates, should have the priority in the management of unfit patients. Chemotherapy, with Docetaxel as the standard regimen, should be reserved to patients showing diffuse symptoms, rapidly increasing PSA and/or presence of visceral metastasis, after all steps of endocrine therapy were covered.

As regard the second line, a number of possibilities are available, but none have been tested in vulnerable and frail patients.

At the present a number of issues about prostate cancer in unfit senior adults patients are still unsolved and should be debated in the light of results from dedicate prospective trials.

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## Introduction

Prostate cancer represents the most frequent malignancy diagnosed in men, with 186,320 estimated new cases (25%) and 28,650 estimated deaths (10%) in USA in 2008.<sup>1</sup> Prostate cancer is a disease typical of the elderly: median age at diagnosis is 68 years and the incidence exponentially increases with age, showing a peak at 80 years.<sup>2</sup>

Prostate cancer has an extremely long natural history, from the initial screening to the terminal illness, and a large variety of approaches, from watchful waiting to chemotherapy. In sick patients, the problem of life expectancy is relevant since palliation is the only aim of any therapy.

Unfortunately, the paucity of data from large prospective trials prevents the physicians from easily identifying what the best treatment is for this kind of patients.

In this review we tried to summarize the main bibliography available for the management of prostate cancer in elderly, not fit patients.

The PubMed database was searched using the following keywords: prostate cancer, geriatric assessment, elderly, unfit, vulnerable, frail, adjuvant, watchful waiting, metastatic, advanced, surgery, radiotherapy, androgen ablation, chemotherapy, target therapies, palliation. Only the papers published between 1990 and 2008 have been considered.

## Geriatric assessment

*Who are the unfit patients?*

The term “fit” was firstly introduced by Balducci<sup>3</sup> to indicate elderly patients who are functionally independent and without relevant comorbidities, so that they may be candidate to receive the same treatments proposed to younger adults.

Patients classified as “non-fit” at comprehensive geriatric assessment represent an extremely heterogeneous population.

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This kind of patients show different degrees of serious comorbidities, functional impairments, cognitive-deterioration, potential or real malnutrition, depressive diseases and geriatric syndromes that can variously combine into hundreds of different realities.

In order to simplify therapeutical choice and management, unfit patients are classified into two subgroups: vulnerable and frail. In particular frailty condition is associated with >40% 2 years-mortality rate, and it is generally defined by at least one of the following conditions: age  $\geq 85$  years, one or more geriatric syndromes,  $\geq 3$  comorbidities grade 3 (CIRS) or  $\geq 1$  comorbidity grade 4, dependence in basic Activities of Daily Life (ADL). The vulnerable patients are characterized by functional independence in basic activities of daily life, but not in basic activities, and the presence of  $\leq 2$  grade 3 associated disease according to CIRS.<sup>3</sup> They should benefit of geriatric interventions.

*What is the distribution of elderly prostate cancer population by geriatric assessment?*

Unfit patients were reported to represent about 75% of a retrospective series of elderly patients afflicted by various neoplasia.<sup>4</sup> The distribution of prostate cancer patients by geriatric assessment is poorly defined, as this issue was investigated by few small trials referring to different cohorts.

Terret et al. prospectively evaluated sixty PC patients aged  $\geq 70$  years by a mini-comprehensive geriatric assessment.<sup>5</sup> This instrument included the Katz Activities of Daily Life (ADL), the Lawton Instrumental Activities of Daily Life (IADL), Cumulative Illness Rating Scale (CIRS), a search for drug interactions, risk of falls and presence of actual or potential malnutrition, the 30-items geriatric depression scale (GDS), a cognitive evaluation. Eighty-seven percent of patients showed to have at least an impairment of IADL while all patients presented  $\geq 1$  relevant comorbidities.

*What are the recommendations of SIOG?*

There is a relevant evidence that CGA has a positive impact on functionality and reduced hospitalization for elderly people, while only few studies showed both its cost-effectiveness and benefit on survival.<sup>6</sup> Both the guidelines from the National Cancer Centre Network [[www.nccn.org](http://www.nccn.org)] and the International Society of Geriatric Oncology indicate some forms of geriatric assessment as a key-component of basal oncological evaluation for all cancer patients aged  $\geq 70$  years. At this point CGA is still far from being extensively performed, mostly because of paucity of resources and also because of the difficulty to translate its results in a treatment plan. This implies the need for screening tools to discriminate patients the health status of whom requires a comprehensive geriatric assessment.

Since the most frequent critic to CGA is that it is time-consuming, some rapid screening tools were tested. Only “Vulnerable Elders Survey-13” (VES-13) was validated in cohorts for prostate cancer patients. In a pilot study involving 50 elderly patients receiving androgen ablation treatment for systemic PC, baseline VES-13 showed a 72.7% sensitivity and 85.7% specificity for deficits relieved at standard CGA.<sup>7</sup>

Particularly, it should be universally accepted that in unfit patients any rapid screening tool could never substitute a complete multidimensional geriatric assessment, which is the only instrument allowing to reach some of the essential objectives.

The *first goal* is to uncover each possible health problem and remove treatable conditions, such as depression, malnutrition and social barriers, when possible. In that way vulnerable patients showing exclusive reversible impairments, could be readapted to healthy conditions. Subsequently they could receive standard treatment as “fit” elderly patients already do.<sup>8</sup>

The *second goal* is to estimate the individual cancer-independent survival probability in order to answer the following crucial question: will our unfit patient die because of prostate cancer or with prostate cancer?

In a retrospective analysis by Newschaffer et al. 61% of elderly patients with incidental diagnosis of prostate cancer finally died because of comorbidities, with heart disease, other cancers, cerebrovascular disease, chronic obstructive pulmonary disease and pneumonia the most frequent problems. In this cohort patients reporting a Charlson comorbidity index  $\geq 1$  showed 39% less odds of dying because of prostate cancer compared to patients with no comorbidities. On the other hand patients older than 85 years diagnosed with PC were more likely to have other underlying causes of death than patients aged 67–74 years.<sup>9</sup> For oncologists CGA is the only way to estimate the natural life expectancy of single patients when not regularly assisted by expert geriatricians. Walter and Covinsky<sup>10</sup> reported the distribution of senior adults by age class, health status (categorized as 25th percentile-presumably the fit patients; 50th percentile the vulnerable- and the lowest 25th percentile-the frail patients) and life expectancy. Men in good health status presented a life expectancy  $\geq 10$  years until they are 84 years old. Differently, in vulnerable patients aged 70–74 years the average life expectation was 12.4 years and it decreased to 9.3 and 6.7, respectively, in the age range 75–79 and 80–85 years. Predictably, frail patients reported a life expectancy  $\leq 6.7$  years.

The *third goal* of CGA is to estimate the physical and psychological attitude of every patient to tolerate endocrine-therapy and chemotherapy. This information is topic in the treatment decision process, since the quality of life is clearly the most important issue in the management of PC in unfit patients.

## Treatment of localized prostate cancer

### Early prostate cancer (T1a-T2)

In unfit patients with early prostate cancer the treatment choice results from the balance of two parameters: the estimated 10-years prostate-cancer specific mortality and the individual PC-independent chance of survival. The treatment is then necessarily modulated by the patient's attitude towards potential adverse events (Fig. 1).

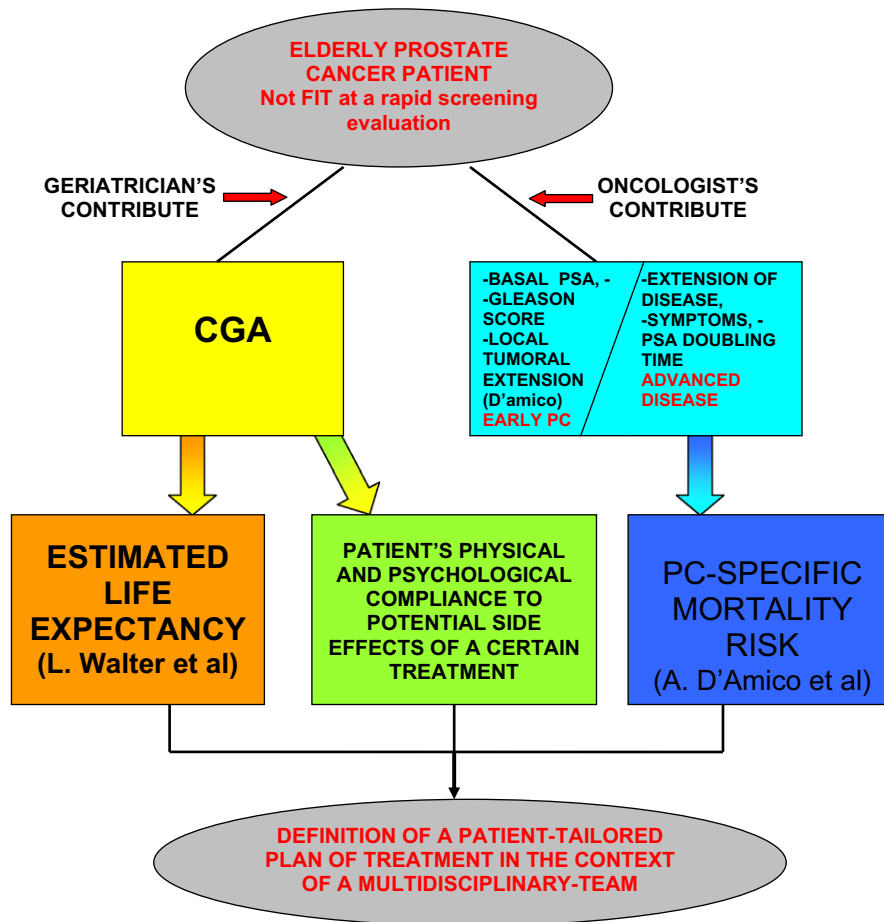
In order to identify pre-treatment risk groups who are at risk of prostate cancer mortality after the treatment, D'Amico et al. reviewed data from a cohort of over 7000 patients treated with radical radiotherapy or with prostatectomy for early prostate cancer between 1988 and 2002.<sup>11</sup> Eventually only high risk patients showed a clinically relevant 10-years mortality due to prostate cancer (60% overall mortality, 30% PC-specific mortality) while in low risk and medium risk group, 10-years mortality due to PC was respectively 0% and 10%.

### Stage T1a-b

For unfit patients with stage T1a-prostate cancer watchful waiting represents the best strategy.<sup>8</sup>

It is generally recognized that patients must have a chance of living approximately 10 years or more to significantly benefit from any upfront active treatment for prostate cancer.<sup>12</sup> Frail patients should never undergo radical prostatectomy nor curative radiotherapy, otherwise they risk to suffer the complications of these treatments without enjoying the consequent, potential survival benefit.

In a cohort of 11,010 men receiving radical prostatectomy between 1990 and 1999, increasing comorbidities were associated with higher risk of complications within 30-days from the surgery.



**Fig. 1.** Decisional tree for elderly unfit prostate cancer patients. Legends: PC, Prostate Cancer; CGA, Comprehensive Geriatric Assessment; PSA, Prostate Specific Antigen.

In addition, after adjustment for comorbidities, age was associated with an increased risk of 30-days mortality.<sup>13</sup>

On the other hand vulnerable patients accepting potential side effects, could be eligible to radical therapy if the following conditions are satisfied: age  $\leq 75$  years, since under this limit the life expectancy for people with average health (50th percentile) is still  $>10$  years<sup>10</sup>; poorly differentiated tumors; geriatric reversible problems that have been solved.

Not even hormonal therapy should be taken in consideration in unfit patients with “incidental” PC, since they would be exposed to long-lasting side effects of androgen deprivation despite the risk of disease progression without treatment after 5 years, which is only 5%.<sup>14</sup>

#### Stage T1c-T2

Even in this group watchful waiting is the optimal option for asymptomatic frail and vulnerable patients having a chance of living less than 10 years and a low or medium 10-years mortality risk related to prostate cancer. It is different for selected younger vulnerable patients with reversible problems and a chance of living more than 10 years after readaptation who could be proposed for curative treatment (radical prostatectomy or radiotherapy) in case of high-risk prostate cancer according to D'Amico classification.<sup>11</sup> However surgery is not indicated when the potential side-effects are important, that is when the risk of incontinence becomes unacceptable (generally at 75 years).

Radiotherapy should sometimes be offered to frail or oldest vulnerable patients having a chance of living more than 5 years and high risk prostate cancer (mainly very high Gleason score).<sup>12</sup>

The RTOG 86-10 trial included 471 patients stage T2-4N0-X M0, of whom 32% had stage T2. Complete Androgen Blockade (CAB), consisting of oral flutamide and goserelin acetate was administered 2 months before irradiation and during irradiation. After a follow up of 8 years, CAB was associated with a benefit in term of local control (42% vs 30%,  $p = 0.016$ ), disease free survival (33% vs 21%,  $p = 0.004$ ) and biochemical disease-free survival (PSA  $< 1.5$  ng/mL, 24% vs 10% ( $p < 0.0001$ )).<sup>15</sup>

Hormonal therapy alone should be considered with palliative intent for unfit, symptomatic patients who have been excluded from any curative treatment. Nevertheless the addition of BAC to radiotherapy does not increase survival in patients with two or more comorbidities. The impact of CAB is thus limited and it adds to side effects.

#### Locally advanced prostate cancer (T3-T4)

In asymptomatic unfit patients with chance of living of less than 10 years who have a well or moderately differentiated T3 prostate cancer (Gleason score less than 8) active treatment should be deferred until a symptomatic progression of the disease occurs.

As reported above, a survival benefit was observed for patients receiving hormonal therapy concomitant to radiotherapy.<sup>15</sup>

#### Biochemical relapse after curative treatment

The timing to start androgen deprivation therapy for biochemical relapse is one of the most debated issue in prostate cancer management. Some authors support watchful waiting as the elective initial approach, since adverse effects of prolonged hormonal

therapy do not counterbalance the survival benefit of an early set out.<sup>16</sup> The EORTC has published a randomized trial of immediate versus deferred androgen deprivation (ADT). Overall survival was slightly better in case of immediate androgen deprivation (fewer deaths not related to PC) but no difference in prostate cancer mortality was reported.<sup>17</sup> Green et al. have assessed the impact of early versus deferred treatment based on the quality of life and cognitive functioning in 62 men with advanced PC. Upfront therapy with LHRH or antiandrogen was significantly associated with sexual dysfunction and negative cognitive effects, while patients undergoing close clinical monitoring reported a higher emotional distress.<sup>18</sup>

Unfit elderly patients, however, should have a major care when potential adverse events appear, in order not to compromise the health status. In this setting, a complete CGA allows to cover the unaddressed problems that can lead to higher risk of developing certain complications.

#### Side effects of androgen deprivation therapy in elderly patients

Androgen deprivation therapy is burdened by a list of side-effects; some are not life-threatening but they significantly impair quality of life.<sup>19,20</sup>

*Vasomotor flushing* was reported to afflict more than 70% of men receiving androgen deprivation<sup>20</sup> and it tends not to disappear during the course of the treatment. Selective serotonin reuptake inhibitors (such as venlafaxine) or gabapentin can significantly reduce this disturb.<sup>21</sup>

*Erectile dysfunctions:* Unfit elderly patients, wishing to preserve their sexual activity represent a minority. In these case the possibility of using an intermittent regimen or substitute LHRH with an anti-androgen should be discussed with the patient. Nevertheless both regimens are not standard treatments (EAU guidelines).

*Gynecomastia* is more frequently associated with combined androgen blockade compared to LHRH analogues alone. Tamoxifen and radiotherapy can be prescribed to alleviate symptoms such as mastodynia.<sup>20</sup>

Other adverse events may be particularly dangerous in unfit patients. For example a close clinical monitoring with preventive measure and, when it is possible, ready treatments is undoubtedly useful to preserve deterioration of physical status and autonomy.<sup>20</sup>

*Osteoporosis:* In men receiving ADT, bone mineral density is reported to decrease by 4%–13% per year, with an exponential increase in the risk of skeletal fractures.<sup>22</sup> In a large cohort of 14,394 patients receiving a 4-years ADT, the prevalence of fractures was 20%.<sup>23</sup> A complete evaluation of bone status should be prescribed at baseline and biphosphonates should be prescribed when T-score  $\leq 2.5$ .<sup>24</sup> In the prospective trial by Michaelson et al. yearly administration of zoledronic acid seemed to significantly prevent the loss of bone mass, with a lower economic impact compared with more frequent administrations.<sup>25,26</sup> The opportunity of delivery prophylactic zoledronic acid in frail patients, should be accurately debated by a geriatric-oncology task force. However, any intravenous treatment with biphosphonates must respect the rules summarized by SIOG.<sup>27</sup> The NCCN have produced specific recommendations for the prevention of ADT induced osteoporosis ([www.nccn.org](http://www.nccn.org)).

*Sarcopenia:* The loss of muscular tissue increases the risk of falls and decrease in ADLs. Balance, mobility, falling risk and malnutrition should be evaluated before starting ADT and, when indicated, physical rehabilitation with slight daily exercises and control of dietary protein intake should be strongly recommended.<sup>28</sup>

*Anemia:* Normochromic, normocytic anemia is frequently associated with ADT, but only in 13% of cases the problem appears relevant.<sup>29</sup> Since anemia may worsen cardio-vascular diseases and induce to the loss of autonomy in ADLs and IADLs, it should be controlled by dietary supplementation (iron and B12-vitamin) or blood-transfusion.

*Cardiovascular-diseases:* Androgen deprivation therapies are associated with increased risk of metabolic syndrome including incident diabetes, coronary heart disease, myocardial infarction and sudden cardiac death.<sup>30</sup> Patients should be assessed for their own cardiovascular risk and monitored during treatment.

*Depression:* ADT is also associated with higher risk of anxious-depressive syndrome, that can significantly damage both the physical and the cognitive status of unfit patients. Geriatric depression scale in the CGA allows to immediately recognize the problem and then refer the patient to the psychologist who may, if necessary, start with the best pharmacologic treatment.<sup>28</sup>

*Cognitive disorders:* Few small studies have explored the association between ADT and cognitive deterioration, producing conflicting results.<sup>31</sup>

*The frailty syndrome:* Androgen deprivation therapy appeared to accelerate the development of frailty in older men with prostate cancer.<sup>32</sup> This effect could be more severe and fast in unfit patients who already present reduced functionality.

#### Treatment of metastatic prostate cancer

With the improvement of life expectancy, despite the frequently slow evolution of PC, patients are more likely to develop metastatic disease in their advanced age.

In elderly unfit patients all steps of endocrine therapy, as LHRH, combination LHRH + antiandrogen, antiandrogen withdrawal should necessarily be ended before starting chemotherapy. Simultaneously, the best supportive care, including bisphosphonates, pain control, corticosteroids, palliative radiotherapy, should be prescribed in order to preserve quality of life.

#### From ADT to chemotherapy in unfit patients: a leap in the dark?

As the disease progresses despite ADT, the choice of the following treatment should be driven by the health status and functionality of the individual patient. This means that health status evaluation is important.<sup>33</sup>

The standard treatment is chemotherapy, Docetaxel being the registered drug in this indication and being the standard regimen.

- As stated in the SIOG guidelines,<sup>8</sup> patients with terminal illness (terminal stage of disease, bedridden, with severe associate diseases and/or relevant cognitive deficits) should receive only symptomatic treatments.
- In healthy senior adults the standard chemotherapy remains the same as in younger patients.
- In frail and vulnerable patients, the later being likely to benefit of rehabilitation after CGA and geriatric intervention, there is no agreement when the chemotherapy should be started. Probably, the largest evidence is in favour of starting chemotherapy only in case of diffuse symptoms (not curable with local measures) and/or rapidly increasing PSA and/or presence of visceral metastasis, because these patients may benefit of the same effects than those obtained when treatment is started earlier. The other question is to decide upon the best weekly or three-weekly regimen, the decision of which is based on the benefit/risk evaluation balance. However, pros and contra of each possibility should be discussed with the patient.

#### Chemotherapy: which standard regimen?

Docetaxel has been proven effective in two randomized trials: in combination with Prednisone<sup>34</sup> and in combination with Est-

ramustine Phosphate and Prednisone<sup>35</sup> compared in both trials to Prednisone only. These trials have demonstrated a benefit of Docetaxel on overall survival, pain relief, analgesic drug consumption and quality of life. These different benefit still remain significant in older versus younger patients, in painful and painless patients. However Estramustine Phosphate induces by itself side effects, as thrombo-embolic diseases, nausea and vomitings as the most frequent; it is the reason why this drug is no more used by the majority of oncologists, particularly in senior adult prostate cancer patients. Thus the standard chemotherapy regimen is Docetaxel 75 mg/m<sup>2</sup> every three weeks and Prednisone 5 mg twice daily. Nevertheless weekly Docetaxel has the same impact on pain, drug consumption and quality of life, but has no impact on overall survival, when compared to Prednisone only. The long-term results of the Docetaxel plus Prednisone trial have been recently published and confirm all these conclusions.<sup>36</sup>

### Chemotherapy: which regimens for unfit senior adult patients?

No specific clinical trial of chemotherapy in metastatic prostate cancer in the senior adult has been performed. Moreover no trial has been designed for unfit patients would have been evaluated through the tools of CGA.

### Vulnerable and frail patients

Only fit and several vulnerable patients after geriatric intervention were likely to be included in the Docetaxel and Prednisone trial<sup>34</sup>: 20% of patients were older than 75 years. However in frail patients the question of using a weekly Docetaxel regimen should be addressed. Data from two phase II trials with weekly docetaxel were retrospectively reviewed in order to analyze the safety and efficacy of such schedule in the elderly. Men aged  $\geq 70$  years showed to achieve similar benefits in terms of PSA response (47% vs 40%), a time of progress and overall survival with comparable grade 3–4 haematological and non-haematological toxicity compared to younger patients.<sup>37</sup> A phase II randomized trial of weekly Docetaxel plus Prednisone versus Prednisone only has shown a survival advantage of the Docetaxel containing arm, the other clinical benefits being the same as in the large three weekly schedules trials.<sup>38</sup> A survey of clinical file of 175 patients aged  $\geq 75$  years receiving first-line Docetaxel either in the 3-weekly (standard) or weekly (adapted) schedule, was recently published.<sup>39</sup> Age  $> 80$  years and PS  $\geq 2$  were strongly associated with the choice of administering the adapted schedule. PSA response rate, median progression free and overall survival were comparable in the two treatment groups. Also grade 3–4 adverse events did not correlate with the schedule, while low PS and presence of visceral metastasis were significantly associated with the adapted regimen. This study has shown that in the routine it seems that there is no major difference in the effect of both regimens, and that the weekly schedule induces less toxicities except fatigue.

The conclusion is that, upon condition of evaluating carefully health status, weekly Docetaxel is a good therapeutic option in selected frail patients with castration refractory prostate cancer.

### Second line

Patients who progress during Docetaxel-based chemotherapy or after interruption, may be eligible to second-line chemotherapy, whose aim is exclusively symptom palliation with minimal toxicity. A number of possibilities are available in this setting, but none have been tested in vulnerable and frail patients. In this case it should be taken great care in the therapeutical choice. When Doce-

taxel has been interrupted after response or stability, it can be reintroduced with benefit on PSA response and symptoms.<sup>40</sup> Other regimens could be discussed on the case by case basis.

### Rehabilitation and geriatric interventions: an essential issue in unfit patients with prostate cancer

Rehabilitation after surgery and radiotherapy for prostate cancer consists in managing urinary incontinence and erectile dysfunction.<sup>41</sup>

The approach for conservative management of urinary incontinence includes pelvic floor muscle training (with or without bio-feedback), electrical stimulation, external compression devices (penile clamps) associated with lifestyle adjustments, and eventual pharmacological treatment. However the value of this approach remains uncertain.<sup>42</sup>

The management of erectile dysfunction is mainly pharmacological (intracavernous injections of vasoactive drugs, PDE5-inhibitors) and surgical (penile prosthetic surgery).<sup>43</sup>

Psychological support and counselling play an important role in both rehabilitations.

These rehabilitation practices, however, are rarely adopted for unfit elderly patients since their compliance and cognitive function are inadequate. They undergo other types of treatment.

In unfit senior adult patients, rehabilitation has an important role in the management of prostate cancer-related disability and even for the consequences of androgen-deprivation therapy. In prostate metastatic cancer with skeletal involvement the main intervention is focused on pharmacological management of pain with analgesic drugs and biphosphonates to counter the consequent immobility syndrome. Orthostatic devices also play an important role in reducing the risk of vertebral collapse and of bone fractures.

Moreover, ADT has known toxicities that can worsen a pre-existing functional decline such as sarcopenia, anemia, metabolic syndrome, decreased bone mineral density, and fatigue.<sup>32,7</sup> This may lead to muscle weakness and osteoporosis<sup>22</sup> with impairment in mobility and static balance, as well as an increasing risk of falls and of fractures.<sup>23</sup> An aerobic exercise program plays an important role in improving physical performance and daily activities, decreasing fatigue and increasing the quality of life.<sup>44</sup>

### Conclusions

Unfit patients represents a heterogeneous and large population in senior adult prostate cancer population.

Each patient deserves a specifically tailored treatment plan. This optimal approach would require a good training of oncologists in geriatric oncology and, above all, the availability of expert geriatricians. Since these conditions are possible only in a few centres worldwide and that prospective trials on senior adult prostate cancer patients are not available so far, the specifically designed guidelines for elderly patients are essential to drive the treatment choice in this delicate population.

SIOG is developing recommendations in senior adults. At each stage of the disease, the decision of treating and how doing should result from the integration of some individual data: the personal chance of living, estimated thank to a complete CGA, the risk of prostate cancer specific mortality, the patient's aptitude to receive a particular treatment and finally patient choice.

A large number of issues about prostate cancer in unfit senior adults patients are far from being solved from the screening to the supportive care and it should be deeply debated in the light of results from prospective trials for unfit senior adult patients.

## Conflict of interest statement

Authors indicated no potential conflicts of interest.

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