Management of Prostate Cancer in Elderly Patients: Recommendations of a Task Force of the International Society of Geriatric Oncology

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\textbf{Abstract}

\textbf{Context:} Prostate cancer is the most frequent male cancer. Since the median age of diagnosis is 66 yr, many patients require both geriatric and urologic evaluation if treatment is to be tailored to individual circumstances including comorbidities and frailty.

\textbf{Objective:} To update the 2014 International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer in men aged >70 yr. The update includes new material on health status evaluation and the treatment of localised, advanced, and castration-resistant disease.

\textbf{Data acquisition:} A multidisciplinary SIOG task force reviewed pertinent articles published during 2013–2016 using search terms relevant to prostate cancer, the elderly, geriatric evaluation, local treatments, and castration-refractory/resistant disease. Each member of the group proposed modifications to the previous guidelines. These were collated and circulated. The final manuscript reflects the expert consensus.

\textbf{Data synthesis:} Elderly patients should be managed according to their individual health status and not according to age. Fit elderly patients should receive the same treatment as younger patients on the basis of international recommendations. At the initial evaluation, screening for cognitive impairment is mandatory to establish patient competence in making decisions. Initial evaluation of health status should use the validated G8 screening tool. Abnormal scores on the G8 should lead to a simplified geriatric assessment that evaluates comorbid conditions (using the Cumulative Illness Score Rating-Geriatrics scale), dependence (Activities of Daily Living) and nutritional status (via estimation of weight loss). When patients are frail or disabled or have severe comorbidities, a comprehensive geriatric assessment is needed. This may suggest additional geriatric interventions.

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Conclusions: Advances in geriatric evaluation and treatments for localised and advanced disease are contributing to more appropriate management of elderly patients with prostate cancer. A better understanding of the role of active surveillance for less aggressive disease is also contributing to the individualisation of care.

Patient summary: Many men with prostate cancer are elderly. In the physically fit, treatment should be the same as in younger patients. However, some elderly prostate cancer patients are frail and have other medical problems. Treatment in the individual patient should be based on health status and patient preference.

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1. Introduction

Prostate cancer is the most frequent male cancer in developed countries [1] and is also common in less developed countries. The median age at diagnosis is 66 yr, and 69% of deaths occur in men aged >75 yr. Since incidence and mortality rise steeply with age, the prostate cancer burden will increase with exponential ageing of the population.

The current paper, which focuses on men aged >70 yr, updates existing International Society of Geriatric Oncology (SIOG) guidelines for the management of elderly prostate cancer patients [2–4]. Issues considered include the risks of both overtreatment and undertreatment and the importance of assessing overall health status, comorbidities, and cognitive function in personalising management. Previously published SIOG guidelines on prostate cancer [3,4] argued that age alone should not preclude effective treatment. Since 2014, the SIOG recommendations have been fully endorsed by the European Association of Urology (EAU) and are now referred to as the EAU/ESTRO/SIOG guidelines [5,6].

The most important new features of these updated guidelines are: (1) the introduction of initial screening for cognitive function; (2) the rewording of health status classification to align with terms currently used in the geriatric literature; (3) consideration of the most important advances in the treatment of advanced prostate cancer and their implications for elderly patients; and (4) a recommendation for the early introduction of palliative management.

Choice of therapy should not be based on chronological age, which proceeds at the same pace for all, but on biological aging and health status, which differ greatly from one person to another. In the USA, a 70-yr-old man in the healthiest 25% of his peers can expect to live 18 yr, while for the frailest 25% life expectancy is only 7 yr [7]. Evaluation of health status is therefore vital to appropriate management. Assessment of social situation is also important and can usefully include whether or not a family care-giver is present, financial resources, and access to services. A further factor, of course, is patient preference, both in relation to the goals of therapy and the means of attaining them.

The gold standard for evaluating health status is the Comprehensive Geriatric Assessment (CGA) [8]. This includes data on demographic, social, functional, nutritional, cognitive, and mental health status; and the presence of comorbidities and geriatric syndromes. It predicts survival and chemotherapy toxicity, identifies reversible conditions, and reflects patients’ capacity to make decisions as well as their values and treatment goals [9]. Although relatively simple, the Activities of Daily Living (ADL) measure of dependency has been used to determine the need for social and healthcare interventions and has prognostic value. Aside from prostate cancer itself, comorbidity is the strongest predictor of death among men with localised disease [10]. The Cumulative Illness Score Rating-Geriatrics (CISR-G) [11] is used to assess comorbidity. In this context, it is helpful to ascertain the stage and potential reversibility of the condition, its history, and the risk of acute organ failure.

However, a CGA is time-consuming and requires specialist staff. Moreover, it is probably needed in only a minority of patients. A rational approach is to screen all patients to identify those who need further assessment. This further assessment can take the form of a simplified geriatric evaluation or a full CGA.

2. Evaluation of health status

Evaluation of health status involves a stepwise process starting with screening using the G8 and mini-COC™ [12]. This is followed, where indicated, by a simplified geriatric assessment and then, again when indicated, by full geriatric assessment, particularly when complex geriatric interventions are needed.

2.1. G8 screening

In a comprehensive review of tools to establish the need for CGA, the G8 (Table 1) was the most robust [8,13]. Thus, a rational approach is to screen with the G8 scale, which was developed specifically for older cancer patients and can be completed in less than 5 min [13]. Its eight components cover food intake, weight loss, body mass index, mobility, neuropsychological problems, polypharmacy, self-perceived health status and age.

In a prospective noninterventional study of almost a thousand men aged >70 yr, an abnormal score on the G8 (<14 on a scale from 0 to 17) strongly predicted mortality over 3 yr and hence a need for full assessment [13]. Following studies showing that the G8 is a good way of identifying patients requiring a CGA, the European Organisation for Research and Treatment of Cancer (EORTC) made G8 screening compulsory for all patients aged >70 yr included in the organisation’s trials. It is also recommended in EAU guidelines.
Screening with G8 has two principal aims: to decide if a CGA is needed to identify reversible conditions that can be addressed by geriatric interventions integrated into the cancer treatment plan [14,15]; and to aid in choosing appropriate prostate cancer treatment (see below).

### 2.2 Cognitive screening

The task force considered that cognitive evaluation was mandatory to assess the patient’s capacity to evaluate information and make informed decisions. This represents an addition to previous guidelines, and one that is likely to assume increasing importance. A recent meta-analysis compared the validity of cognitive screening tools [16]. The authors identified 102 studies that used the Mini Mental State Examination (MMSE). However, this is time-consuming to complete. Of ten alternative tests, the mini-COGTM [12] had a diagnostic performance that most closely matched that of the MMSE, and was chosen. A cutoff point of ≤3/5 indicates a need to refer the patient for full evaluation of potential dementia (Table 2).

### 2.3 Simplified geriatric evaluation

Patients with an abnormal G8 score (≤14/17) should have a simplified geriatric evaluation (Table 3). This consists of the ADL measure of dependence, the CIRS-G to assess comorbidities, and weight loss as an indication of malnutrition. This may determine firstly whether specific geriatric interventions are needed, and secondly whether a full CGA is required.

#### 2.3.1 Dependence

Dependence is typically evaluated using the ADL scale [17,18]. The presence of one ADL impairment—with the exception of incontinence—is considered abnormal [2]. The presence of more than two ADL impairments is unlikely to be reversible.

#### 2.3.2 Comorbidities

The CIRS-G [11] is a good tool for assessing the risk of non-prostate cancer death [2,11]. The CIRS-G, which rates nonfatal conditions according to their severity and degree of control by treatment, is subjective but practical [19]. The task force judged that geriatric interventions following a CGA are likely to reverse grade 2 comorbidities. Single grade 3 comorbidities are generally irreversible, but need to be individually evaluated. Grade 4 comorbidities are, by definition, irreversible.

#### 2.3.3 Nutritional status

Malnutrition increases mortality in elderly patients [20] but, unless severe, may be reversible via geriatric intervention. The task force decided to screen for malnutrition using weight loss during the last three months. Good nutritional status is defined as <5% loss; risk of malnutrition as loss between 5% and 10%; and severe malnutrition as weight loss >10%.

### 3 Categorisation of patients and implications for treatment

It is generally argued that candidates for definitive therapy for localised prostate cancer should have a life expectancy of ≥10 yr. In metastatic castration-resistant prostate cancer (mCRPC) it is important to assess 2-yr and 5-yr survival. Available tools can predict 1-yr or 5-yr survival for patients living at home or in hospital or nursing home settings [21], but no classification or prognostic model based on health status has been validated in urologic oncology. Recent
Step 1: Three words registration

Look directly at person and say, “Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now.” If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies. For repeated administrations, use of an alternative word list is recommended.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Banana</td>
<td>Leader</td>
<td>Village</td>
<td>River</td>
<td>Captain</td>
<td>Daughter</td>
</tr>
<tr>
<td>Sunrise</td>
<td>Season</td>
<td>Kitchen</td>
<td>Nation</td>
<td>Garden</td>
<td>Heaven</td>
</tr>
<tr>
<td>Chair</td>
<td>Table</td>
<td>Baby</td>
<td>Finger</td>
<td>Picture</td>
<td>Mountain</td>
</tr>
</tbody>
</table>

Step 2: Clock drawing

Say: “Next, I want you to draw a clock for me. First, put in all of the numbers where they go.” When that is completed, say: “Now, set the hands to 10 past 11.” Use a preprinted circle for this exercise. Repeat the instructions as needed, as this is not a memory test. Move to Step 3 if the clock is not complete within 3 min.

Step 3: Three words recall

Ask the person to recall the three words you stated in Step 1. Say: “What were the three words I asked you to remember?” Record the word list version number and the person’s answers.

Scoring

Word recall: ______ (0–3 points)

=1 point for each word spontaneously recalled without cueing.

Clock draw: ______ (0 or 2 points)

=Normal clock: 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6, and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored.

Inability or refusal to draw a clock (abnormal) = 0 points.

Total score: ______ (0–5 points)

=Total score: word recall score + clock draw score.

A cut point of <3 on the Mini-COG™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

Table 3 – Summary of the different steps in health status evaluation and estimated time required

<table>
<thead>
<tr>
<th>Step</th>
<th>Tools</th>
<th>Time</th>
<th>Who can do it</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory initial step</td>
<td>G8</td>
<td>5 min</td>
<td>Trained nurse</td>
</tr>
<tr>
<td>Simplified geriatric evaluation if G8 score ≤14</td>
<td>Mini-COG™</td>
<td>5 min</td>
<td>Trained nurse</td>
</tr>
<tr>
<td></td>
<td>ADL</td>
<td>1 min</td>
<td>Trained nurse</td>
</tr>
<tr>
<td></td>
<td>CIRS-G</td>
<td>15 min</td>
<td>Trained nurse and/or doctor</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>1 min</td>
<td>Trained nurse</td>
</tr>
<tr>
<td>Comprehensive geriatric assessment if geriatric intervention needed</td>
<td>Screening tools and complete clinical examination</td>
<td>2 h to 1 d in hospital</td>
<td>Geriatrician + other health professionals</td>
</tr>
</tbody>
</table>

Table 2 – The Mini-COG™ screening tool. Copyright S. Borson, reprinted with permission of the author (soob@uw.edu). [12]

recommendations are to estimate life expectancy based on the combination of age and comorbidity [22,23]. Therefore, the choice remains pragmatic and open to debate. However for future research better tools are desirable. It is vital that decision-making is shared with patients and that they receive detailed information, including assessment of potential risks and benefits [24].

Health status in SIoG guidelines has generally been defined according to groups described by Baldacci and Extermann in 2000 [25]. These revised prostate cancer guidelines classify patients into four groups (the terminology now aligns with that in the geriatric literature) along with the implications for treatment (Figs. 1 and 2).

1. Healthy or fit: G8 score >14. Patients are expected to tolerate any form of standard treatment. The choice of a particular local treatment is then based on the patient’s wishes and the risk of specific side effects, such as incontinence (described below), for each modality.

2. Frail: patients with a G8 score ≤14 but whose problems, as established via a simplified geriatric assessment (CIRS-G, ADL, and malnutrition), are considered reversible. Such problems are: one or two reversible deficiencies in ADL (apart from incontinence); CIRS-G grade 2 comorbidities (a single grade 3 comorbidity may also be reversible); and weight loss of 5–10%. Patients whose problems are reversed can be considered fit for standard prostate cancer therapies.

3. Disabled or with severe comorbidities: nonreversible problems. These include more than two ADL deficiencies; multiple grade 3 comorbidities on the CIRS-G or any grade 4 comorbidity; or weight loss >10%. Such patients should be managed symptomatically. Certain patients may benefit from geriatric interventions indicated after CGA and can be given specific adapted cancer treatments.

4. Terminally ill: palliation only.

Two additional points should be made. First, in patients who require a CGA, specific geriatric interventions may be suggested. Second, if the mini-COG™ score is abnormal, a full neuropsychological assessment is recommended.
Screening with G8 and mini-COG™

Score >14
No simplified geriatric evaluation is needed

Score ≤14
Simplified geriatric evaluation is mandatory

Reversible =
- Abnormal ADL: 1 or 2
- Weight loss 5–10%
- Comorbidities CIRS-G grades 1–2

Nonreversible =
- Abnormal ADL: ≥ 2
- Weight loss >10%
- Comorbidities CIRS-G grades 3–4

Fit

Frail

Disabled/severe comorbidities

CGA then geriatric intervention

Geriatric screening with G8 tool and mini-COG™
Then simplified geriatric evaluation if G8 ≤14

Group 1
(healthy)

Group 2
(frail, ie, reversible problems)

Group 3
(disabled/severe comorbidities, ie, nonreversible problems)

Group 4
(terminal illness)

Principles = early introduction of palliative care

Standard treatment as for younger patients

Standard treatment as for younger patients

Symptomatic management including adapted specific treatments

Only palliative treatments

CGA then geriatric intervention

CGA then geriatric intervention

Fig. 1 – Decision tree to determine patient health status. mini-COG™ = mini-COG™ cognitive test; ADL = Activities of Daily Living; CIRS-G = Cumulative Illness Rating Score-Geriatrics; CGA = Comprehensive Geriatric Assessment.

Geriatric screening with G8 tool and mini-COG™
Then simplified geriatric evaluation if G8 ≤14

Group 1
(healthy)

Group 2
(frail, ie, reversible problems)

Group 3
(disabled/severe comorbidities, ie, nonreversible problems)

Group 4
(terminal illness)

Principles = early introduction of palliative care

Standard treatment as for younger patients

Standard treatment as for younger patients

Symptomatic management including adapted specific treatments

Only palliative treatments

CGA then geriatric intervention

CGA then geriatric intervention

Fig. 2 – Decision-making based on health status assessment. mini-COG™ = mini-COG™ cognitive test; CGA = Comprehensive Geriatric Assessment.

The task force also had a number of specific recommendations. First, prospective studies should be initiated to validate screening tools in elderly prostate cancer patients. The G8 in particular should be validated in this specific population. Second, prospective studies to validate this pragmatic classification should follow establishment of consensus among oncogeriatrians. Third, nomograms should be developed to predict outcome in older prostate cancer patients in different settings when using tools that assess health status (comorbidities through CISR-G, dependence, and malnutrition).

4. Treatment of elderly prostate cancer patients

We examined standard management of localised and advanced disease and applied when possible considerations specific to elderly men.

4.1. Localised disease

Treatment is based on risk [26]. In a large study [27], mortality at 15 y was independent of age at diagnosis but directly linked to risk group, ranging from 10% (low risk) to 20% (intermediate risk) and 35–40% (high risk). Non-prostate cancer mortality was mainly linked to comorbidities, but the aggressiveness of the disease outweighed comorbidity in intermediate- and high-risk groups. The aim in T1–3N0M0 disease is generally curative. Decisions in the elderly should take into account the risk of dying from prostate cancer (ie, tumour grade and stage), the risk of dying from another cause (ie, comorbidities), the risks of treatment, and patient preferences.

Healthy elderly patients with high-risk prostate cancer are often undertreated. However, there is also concern about the overtreatment of many low-risk patients with comorbidities and limited life expectancy [2]. It is important to assess both oncologic outcomes (extracapsular disease, metastases, lymph node invasion, and cancer-specific death) and functional outcomes (eg, erectile dysfunction and incontinence).

4.1.1. Radical prostatectomy (RP)

Older men are more likely to have larger and higher-grade tumours [28], and thus might benefit more from a local treatment including RP. For high-risk lesions, cancer-specific survival is up to 91% after surgery combined with adjuvant and/or salvage modalities. Survival can be up to 95% with one risk factor (ie, Gleason ≥7, stage ≥T2, or prostate-specific antigen [PSA] >20 ng/ml), and 79% with three risk factors [29].

We do not know whether surgery should be open or minimally invasive. A recent review suggested that in older patients, a minimally invasive approach led to higher rates of transfusion, postoperative genitourinary complications, incontinence, and stricture when compared to the same procedure in younger men [30].

Although 30-d mortality after RP increases with age, it is only 0.66% in men aged 70–79 yr [31]. Death and complications following RP depend more on comorbidities. Conversely, incontinence and erectile dysfunction are predominantly influenced by age [31]. Even so, continence rates are still good in older men, with 86% aged ≥70 yr regaining continence [31]. Recent data on robotic prostatectomies do not reveal any difference in complications and continence between patients aged <70 and ≥70 yr. Only potency recovery was better among younger patients. An Australian cohort compared continence after robotic RP in men <70 and ≥70 yr and found no difference [32].

4.1.2. Radiation therapy

Image-guided intensity-modulated radiotherapy (RT) is now standard for external-beam RT. Evidence is accumulating regarding brachytherapy (low and high dose rates) as a “boost” or as monotherapy.

Combined RT and androgen deprivation therapy (ADT) is standard for locally advanced or intermediate- to high-risk T1/T2 disease. The optimum duration of ADT with higher-dose RT is yet to be determined. Adding ADT to RT confers no benefit to patients with localised high-risk prostate cancer and competing moderate to severe comorbidities, as the latter have a greater impact on survival than the cancer [33].

Age does not increase acute or late urinary or bowel toxicity, but does predict reduced sexual function. However, 90% of patients surveyed about their treatment would make the same decision if asked again [34].

In the CHHIP study, standard RT fractionation (37 fractions over 7.5 wk) was compared to a hypofractionated regimen (20 fractions over 4 wk). Most patients had intermediate-risk disease. Acute bowel toxicity was greater with hypofractionation, but other acute and late toxicities were comparable. At 5 yr the biochemical control rate was not inferior to standard fractionation and actually favoured patients aged >69 yr [35].

4.1.3. Neoadjuvant/adjuvant treatment

The GETUG 12 trial [36] reported on ADT plus docetaxel and estramustine versus ADT alone in patients (median age 62–64 yr) with treatment-naive prostate cancer and at least one risk factor. However no data were presented that relate specifically to elderly patients.

4.1.4. Minimally invasive therapies

Hemi-gland ablation or ablation of the index lesion(s) may provide well-tolerated control in the elderly at low to intermediate risk, but at present remains experimental. Options include high-intensity focused ultrasound, cryo-therapy, brachytherapy, photodynamic and laser therapy, and irreversible electroporation.

4.1.5. Androgen deprivation therapy

In patients with high-risk nonmetastatic prostate cancer who are too frail to receive curative treatment, immediate ADT has a very modest role [37]. It improves overall survival (OS; hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.05–1.39), but not cancer-specific survival. If not initially treated with ADT, the median time to start ADT on the basis of symptoms was 7 yr, and 44% of patients in the deferred
arm never received ADT. It was suggested that only those with initial PSA >50 ng/ml or a PSA doubling time <12 mo with PSA of 8–50 ng/ml were at higher risk of death. Three major randomised trials have clearly demonstrated that ADT alone is inferior to ADT plus RT in terms of prostate cancer-specific survival [38–40]. ADT may be palliative in patients too sick or frail for a local treatment combined with ADT. However, ADT alone must be considered under-treatment since the survival benefit of combination with RT is evident even after 6–7 yr [41]. The combination also reduces local progression and associated side effects. However, ADT increases the risk of fractures, cognitive impairment, diabetes, thromboembolic events, and all-cause mortality in patients with a history of cardiovascular disease [2].

4.1.6. Watchful waiting and active surveillance

Patients with low-risk disease are likely to benefit from watchful waiting (ie, expectant management) or active surveillance with curative intervention delayed until progression.

SIOG recommendations for the management of localised prostate cancer in elderly patients are summarised in Table 4.

4.2. Advanced prostate cancer

4.2.1. Metastatic hormone-naive prostate cancer

Until 2014, ADT was the mainstay of treatment. Recently, three studies (GETUG-AFU-15 [42], CHAARTED [43], and STAMPEDE [44]) assessed the efficacy and tolerability of ADT with or without docetaxel in metastatic hormone-naive prostate cancer. All included some patients who developed metastases following local treatment, but the majority had de novo metastatic disease. A meta-analysis [45] revealed that addition of docetaxel to the standard of care improved survival. The HR of 0.77 (95% CI 0.68–0.87; p < 0.0001) translates into a 9% absolute improvement in 4-yr survival. Adding docetaxel to ADT also improved failure-free survival (HR 0.64; p < 0.0001), translating into a reduction in absolute 4-yr failure rates of 16% (95% CI 12–19%). The addition of docetaxel to ADT should be considered the new standard of care for men suitable for chemotherapy with M1 hormone-sensitive prostate cancer starting treatment for the first time. Zoledronic acid does not significantly improve survival or decrease the incidence of skeletal-related events in this setting [44].

The median age in all three trials was <67 yr. We therefore need more information on whether the results of chemohormonal therapy can be extrapolated to elderly patients. It is likely that patients with metastatic prostate cancer, especially those with high-volume disease, who are fit to receive docetaxel in addition to ADT may benefit from such a regimen. However the risk/benefit balance should be discussed carefully with each patient.

4.2.2. Metastatic castration-resistant prostate cancer

When prostate cancer becomes resistant to castration, ADT should be continued, but no available data support this approach in elderly patients specifically. Care should be taken to prevent an increase in the risk of osteoporosis and fracture [4].

<table>
<thead>
<tr>
<th>Table 4 – International Society of Geriatric Oncology recommendations for the management of prostate cancer in elderly patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment should be based on health status (mainly severity of associated comorbidities) rather than age, and on patient preference</strong></td>
</tr>
<tr>
<td><strong>Localised disease</strong></td>
</tr>
<tr>
<td>• Fit and frail patients in the D’Amico high-risk group with a chance of surviving &gt;10 yr are likely to benefit from treatment with curative intent</td>
</tr>
<tr>
<td>• Patients at low- to intermediate-risk are likely to benefit from active surveillance or watchful waiting, based on their individual expected survival. A curative approach must be discussed with intermediate-risk patients who have the longest expected survival</td>
</tr>
<tr>
<td>• The balance of benefits and harms of ADT for localised prostate cancer should be carefully assessed. Note the higher risk of diabetes, cardiovascular complications, osteoporosis, bone fractures, and cognitive dysfunction</td>
</tr>
<tr>
<td><strong>Advanced disease</strong></td>
</tr>
<tr>
<td>• ADT plus six cycles of docetaxel is the recommended first-line treatment in fit men with newly diagnosed hormone-sensitive metastatic prostate cancer. It is also appropriate (especially in the setting of high-volume disease) in some frail patients, but detailed information should have been collected in a CGA and comorbidities treated. In all other cases ADT alone remains the standard</td>
</tr>
<tr>
<td>• Patients treated with ADT should have their bone mineral status evaluated and should receive calcium supplementation (if dietary intake is insufficient) and vitamin D. In those at high risk of osteoporosis, use of bisphosphonates/denosumab is recommended</td>
</tr>
<tr>
<td>• In mCRPC, docetaxel 75 mg/m² every 3 wk is suitable for both fit and “frail” senior adults, while the biweekly regimen should be considered in those who are disabled or have severe comorbidities</td>
</tr>
<tr>
<td>• In mCRPC, abiraterone and enzalutamide are suitable first-line options</td>
</tr>
<tr>
<td>• In patients who have received docetaxel, options include cabazitaxel, abiraterone, and enzalutamide</td>
</tr>
<tr>
<td>• The optimum sequencing of therapies is subject to research. After failure of a novel endocrine agent, agents with another mechanism of action including taxanes or radium-223 should be the preferred option because of cross-resistance between androgen receptor–targeted agents</td>
</tr>
<tr>
<td>• Careful evaluation of drug-drug interactions and proactive management of adverse events is needed in senior adults</td>
</tr>
<tr>
<td>• Patients (with no visceral or bulky lymph node metastases) receiving first-line treatment for mCRPC, and after failure to docetaxel, are eligible for radium-223</td>
</tr>
<tr>
<td>• Palliative treatments include radiotherapy, radiopharmaceuticals, bone-targeted therapies, palliative surgery, and medical treatments for pain and symptoms</td>
</tr>
<tr>
<td>• Early palliation should be implemented</td>
</tr>
<tr>
<td>• Management of the patient and family should include a multidisciplinary approach (Urologist, medical oncologist, radiation oncologist, geriatrician, nurse and palliative medicine specialist)</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; mCRPC = metastatic castration-resistant prostate cancer; CGA = Comprehensive Geriatric Assessment.

4.2.2.1. Cytotoxic chemotherapy. There is increasing evidence that older age per se is not a contraindication to chemotherapy. Docetaxel 75 mg/m² every 3 wk plus daily prednisone is the standard of care in CRPC [4], improving OS while reducing pain and improving quality of life when compared to mitoxantrone plus prednisone. The OS benefit for men aged ≥75 yr was similar to that for younger patients, but there were more G3/4 toxicities and dose reductions [4]. A two-weekly docetaxel regimen was associated with an increase in OS of 2.5 mo, and fewer cases of grade 3–4 neutropenia compared with a three-weekly regimen [46]. In a prospective registry study in patients aged ≥70 yr, those with frailty related to cancer also benefited from a taxane-based therapy (regimen adapted in 52%) [47].

Cabazitaxel is combined with prednisone in patients progressing during or after a docetaxel-based regimen [4]. Safety was analysed by age (<70, 70–74, and ≥75 yr) among 746 men [48]. The number of cabazitaxel cycles, dose reductions for any cause, dose delays possibly related to cabazitaxel adverse events, and tolerability were similar in the three age groups. Prophylactic granulocyte colony-stimulating factor (G-CSF) use was more common in men aged ≥70 yr. In multivariate analysis, age ≥75 yr, first treatment cycle, and baseline neutrophil count <4000/mm³ were associated with higher risk of grade ≥3 neutropenia and/or neutropenic complications. Prophylactic G-CSF reduced this risk by 30% (odds ratio 0.70; p = 0.04). A recent phase 3 study comparing cabazitaxel 20 mg/m² versus 25 mg/m² every 3 wk plus daily prednisone in mCRPC patients progressing after docetaxel concluded that 20 mg/m² was noninferior in terms of OS and was better tolerated [49].

The toxicity of chemotherapy in older patients can be predicted. Two published models use somewhat different criteria, but geriatric, chemotherapy, and biological characteristics are predictive in both [4]. Severe toxicity rates were relatively high with both models, indicating that older patients should be monitored closely. There is strong evidence to support primary prophylaxis with G-CSF in this setting [4]. Alternatively, the chemotherapy regimen could be adapted.

4.2.2.2. Endocrine therapies. Abiraterone in combination with prednisone is effective in both chemotherapy-treated and chemotherapy-naive mCRPC patients [4,50]. In chemother-apy-naive mCRPC, median OS was significantly longer in the abiraterone plus prednisone group than for placebo plus prednisone (34.7 vs 30.3 mo; HR 0.81; p = 0.0033) [50]. Elderly patients in both treatment arms had higher rates of fluid retention and cardiac disorders than younger patients, although dose reductions or treatment interruptions due to adverse events were few in both groups. Abiraterone demonstrated clinical benefit and was well tolerated in elderly men with chemotherapy-naive mCRPC. Thus, abiraterone is also an option for patients who may not tolerate therapies with higher toxicity.

Enzalutamide increased OS compared to placebo in the postchemotherapy setting in mCRPC (AFFIRM trial) [4,51]. The effect in elderly patients was similar to that in the total study population, but some side effects were more common [52]. In the PREVAIL trial, oral enzalutamide 160 mg/d was compared to placebo in chemotherapy-naïve mCRPC [53]. Some 72% of men in the enzalutamide group but only 63% in the placebo group were alive at cutoff (29% reduction in risk of death; HR 0.71; p < 0.001). Fatigue and hypertension were the most common adverse events associated with enzalutamide. Among patients aged >75 yr (35% of the total), the median treatment duration was 16.6 and 5.0 mo in the enzalutamide and placebo arms, respectively [54]. In the elderly subgroup, OS was greater for enzalutamide than for placebo (32.4 vs 25.1 mo; HR 0.61; p = 0.0001), that is, elderly men benefited from enzalutamide, which was generally well tolerated, but fatigue and falls may be related side effects. Since enzalutamide is a strong CYP3A4 inducer, drug interactions should be carefully checked.

4.2.2.3. Treatment sequencing. Progression on one of the novel hormonal agents is usually associated with poor response to subsequent use of another one. The optimum sequencing of life-extending therapies has not been determined [55].

Symptomatic patients with mCRPC—both fit and frail—should receive first-line docetaxel, while those who are disabled or have severe comorbidities or are reluctant to receive chemotherapy should receive novel endocrine agents. At progression after docetaxel, cabazitaxel and novel endocrine agents are appropriate for fit patients. Chemotherapy-naïve fit patients who have experienced failure on a novel endocrine agent should receive second-line taxane chemotherapy since cross resistance means they are unlikely to respond to a second endocrine agent. Patients need to be fully informed of the benefits and side effects so that they can indicate a preference.

4.2.2.4. RT/radiopharmaceuticals and bone-targeted therapy. RT is the first-choice treatment for localised painful metastasis in elderly men with prostate cancer. A phase 3 study of patients with painful metastases and no visceral metastases who had progressed after docetaxel or who were unfit for or unwilling to have chemotherapy compared Ra-223 with placebo [4]. Ra-223 extended OS, delayed skeletal-related events, and improved quality of life in older and younger patients. Therefore, patients without visceral or bulky lymph node metastases who are receiving first-line treatment for mCRPC after failure of docetaxel are eligible to receive Ra-223.

In patients with newly diagnosed metastatic or nonmetastatic prostate cancer, adding zoledronic acid to ADT did not benefit failure-free survival, skeletal-related events, or OS [44]. In CRPC and bone metastases, zoledronic acid (4 mg intravenously) or denosumab (120 mg subcutaneously) every 4 wk is recommended to decrease the risk of disease-related skeletal complications such as pathologic fractures. Both drugs have been approved by the US Food and Drugs Administration and the European Medicines Agency in this setting [4]. Preventive measures (calcium and vitamin D supplementation, and an initial dental check) are of utmost importance [4].
4.2.2.5. Immunotherapy. New therapies for mCRPC include immunotherapy [4]. None is currently available outside the USA.

4.2.2.6. Palliative care. Life expectancy of <1 yr defines a patient who might benefit from a palliative care approach [56]. Temel et al [57] deserve credit for demonstrating that it is possible to include early specialized palliative care in the management of advanced cancer and that patients are best served by management that combines cancer and palliative care specialists. The major benefits were lower anxiety and depression, better quality (and quantity) of life, and less time spent in hospital. These studies were in lung cancer, and similar research should be conducted in prostate cancer, for which the burden of symptoms, especially in the elderly, can be very high.

Task force recommendations for the management of advanced prostate cancer in elderly patients are summarised in Table 4.

5. Conclusions

A SIOG prostate cancer task force has updated recommendations for the management of elderly men with prostate cancer. Overall, the urologic approach in the fit elderly should be the same as in younger patients and based on existing international recommendations. Individual elderly patients should be managed according to their health status and not according to age.

Evaluation of health status should include a validated screening tool (the G8) and the assessment of comorbid conditions (CIS-R-G scale), degree of dependence (ADL), and nutritional status (weight loss estimation). When patients are frail or disabled or have severe comorbidities, a CGA is needed. This may indicate the need for additional geriatric interventions. Screening for cognitive impairment is mandatory when making treatment decisions and should be part of the initial patient assessment.

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