



## Review

# Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients



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**Abstract** **Background:** The median age of prostate cancer diagnosis is 66 years, and the median age of men who die of the disease is eighty years. The public health impact of prostate cancer is already substantial and, given the rapidly ageing world population, can only increase. In this context, the International Society of Geriatric Oncology (SIOG) Task Forces have, since 2010, been developing guidelines for the management of senior adults with prostate cancer.

**Material and methods:** Since prostate cancer and geriatric oncology are both rapidly evolving fields, a new multidisciplinary Task Force was formed in 2018 to update SIOG recommendations, principally on health status screening tools and treatment. The task force reviewed pertinent articles published between June 2016 and June 2018 and abstracts from European Association of Urology (EAU), European Society for Medical Oncology (ESMO), American

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Society of Clinical Oncology (ASCO) and American Society of Clinical Oncology Genito-urinary (ASCO GU) meetings over the same period, using search terms relevant to prostate cancer, the elderly, geriatric evaluation, local treatments and advanced disease. Each member of the group proposed modifications to the previous guidelines. These were collated and circulated. The final manuscript reflects the expert consensus.

**Results:** The 2019 consensus is that men aged 75 years and older with prostate cancer should be managed according to their individual health status, and not according to age. Based on available rapid health screening tools, geriatric evaluation and geriatric interventions, the Task Force recommends that patients are classified according to health status into three groups: (1) ‘healthy’ or ‘fit’ patients should have the same treatment options as younger patients; (2) ‘vulnerable’ patients are candidates for geriatric interventions which—if successful—may make it appropriate for them to receive standard treatment and (3) ‘frail’ patients with major impairments who should receive adapted or palliative treatment. The 2019 SIOG Task Force recommendations also discuss prospects and unmet needs for health status evaluation in everyday practice in older patients with prostate cancer.

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## 1. Introduction

Prostate cancer is the fourth most frequent cancer worldwide [1]. In more developed regions, the age-standardised incidence per 100,000 is 68 and the age-standardised mortality is 10 per 100,000 [2]. Sixty percent of patients are aged 65 years and older at diagnosis. This proportion will increase to 70% by 2040. Moreover, the total number of patients with prostate cancer aged 70 years and older will increase between 2018 and 2030 from 585,000 to 778,000 [3]. Over the same period, prostate cancer deaths in men aged 70 years and older are expected to almost double, while the overall mortality rate is anticipated to be stable [1]. Although the median age at prostate cancer diagnosis is 66 years, the median age of men who develop metastatic disease is considerably older, and the median age of those who die from the disease is eighty years (Fig. 1) [4]. The public health burden of treating older men with both early and late prostate cancer is already substantial and will increase over the coming decades.

Since 2010, the International Society of Geriatric Oncology (SIOG) has produced several guidelines on

prostate cancer management in older patients [5–8]. Although the literature reviews on which these guidelines were based were not systematic, they represented an expert multidisciplinary consensus. A major part of their purpose was to introduce the basics of geriatric frailty screening into urology and oncology departments. These guidelines used an age of 70 years to define older patients.

The first SIOG article [5] reviewed the most important geriatric factors used in the process of making treatment decisions, i.e. dependence, comorbidities and nutritional status. Its most important conclusion was that treatment should not be based on chronological age but on health status as established by screening using different tools and evaluated by comprehensive geriatric assessment (CGA). The Task Force also introduced the concept of geriatric intervention. This led, the same year, to the first set of SIOG recommendations [6].

The updated 2014 guidelines [7] introduced the G8 screening tool [9] to identify patients likely to benefit from a simplified geriatric evaluation or, in some cases, from a CGA in a geriatric unit.

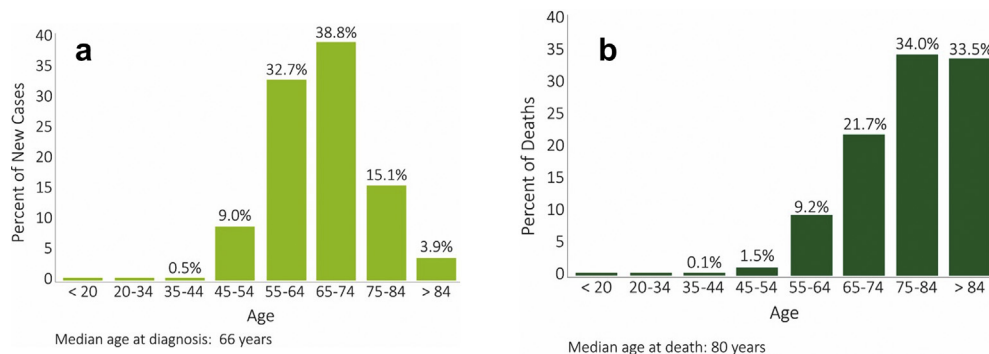


Fig. 1. Age distribution at (a) diagnosis and (b) death. SEER Cancer Stat Facts4: Prostate Cancer. National Cancer Institute. Bethesda, MD, <https://seer.cancer.gov/statfacts/html/prost.html>.

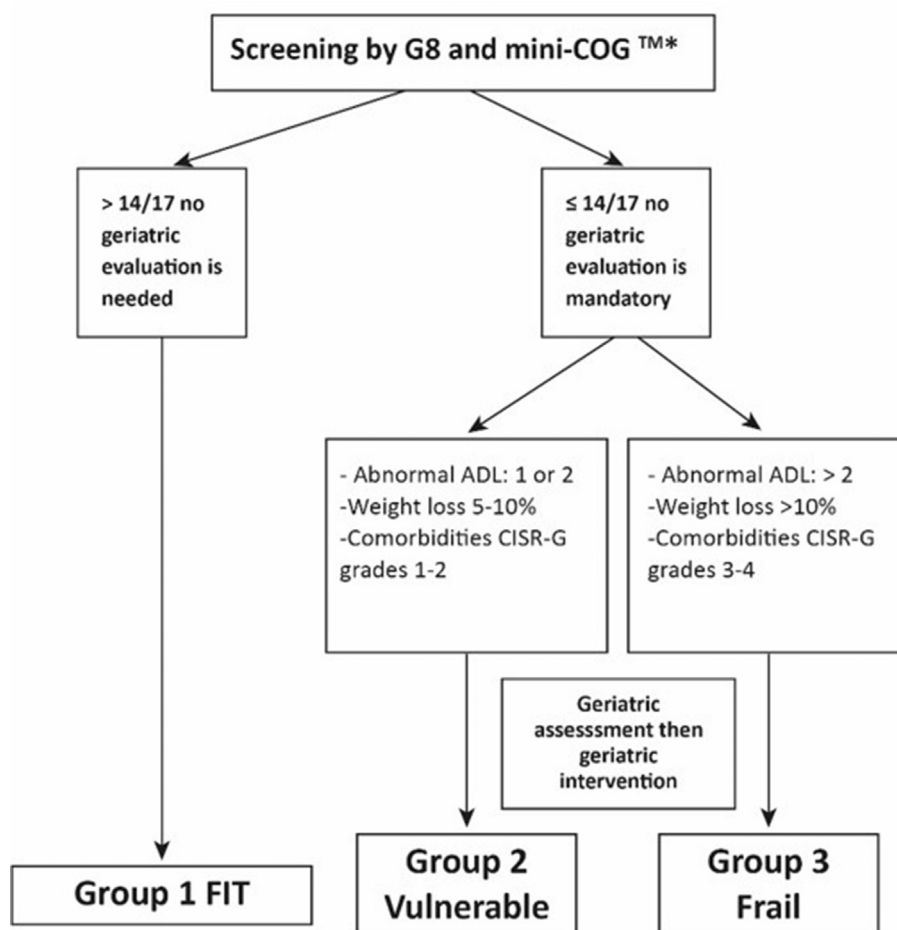


Fig. 2. Decision tree to determine patient health status [8]. Mini-COG™, Mini-COG™ cognitive test; ADLs, Activities of Daily Living; CIRS-G, Cumulative Illness Rating Score – Geriatrics; CGA, comprehensive geriatric assessment. For Mini-COG™, a cut-off point of ≤3/5 indicates a need to refer the patient for full evaluation of potential dementia.

The 2017 update incorporated two important aspects not previously considered: the screening of cognitive impairment (using the Mini-COG™ tool) and the early introduction of palliative care [8].

A second important step was the full endorsement of the SIOG guidelines by the European Association of Urology, such that the recommendations are now referred to as the EAU/ESTRO/SIOG guidelines. The year 2017 also saw the dissemination within the urological community of a statement on the role of geriatric oncologists in optimising care of urological oncology patients [10]. In this context, we can note that the EAU and SIOG are also currently cooperating with guidelines on the management of bladder cancers in older patients.

Because prostate cancer and geriatric oncology are both rapidly evolving fields, SIOG in 2018 convened another Task Force. This had the aims of updating information on the active management of advanced prostate cancer and in supportive care and discussing likely developments in management. This latter topic was broad and included surgery, minimally invasive therapies and surveillance, external beam radiotherapy

(EBRT) and brachytherapy, review of health status evaluation and geriatric oncology considerations in low- and middle-income countries. These guidelines are shown in Table 1.

Chairs of the SIOG Task Force performed searches via MEDLINE and PubMed using the terms ‘prostate cancer’, ‘neoplasms’, ‘elderly’, ‘age limit >70 years’ and ‘metastatic prostate cancer’. Articles selected were in English, focussing on the period since 01/06/2016 (the cut-off date of the literature search for the 2016 SIOG guidelines [8]) to 30/06/2018. One hundred eighty-five articles were selected based on abstract review. Section authors chose from this selection and added articles and abstracts they considered significant. Abstracts of the following meetings were also reviewed for relevant studies: EAU, ESMO, ASCO-GU and ASCO 2017 and 2018 annual meetings.

The members of the writing committee developed a first draft which was commented on by the reviewing committee and amended. Consensus was reached by the review process between July and August 2018. All authors approved the final version.

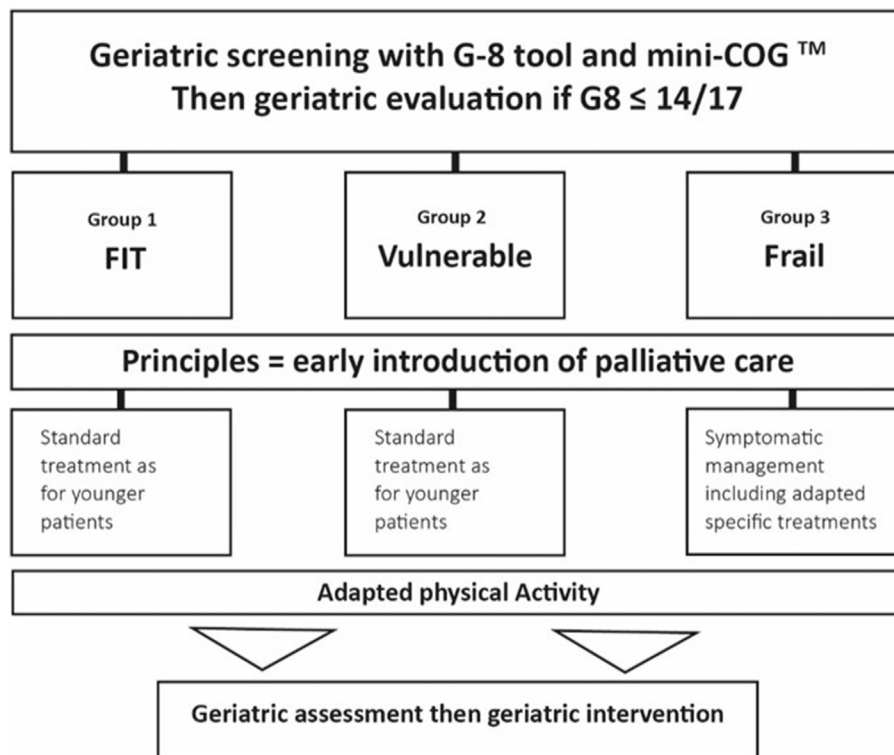


Fig. 3. Decision-making based on health status assessment [8]. G8; Mini-COG™, Mini-COG™ cognitive test; CGA, comprehensive geriatric assessment. For Mini-COG™, a cut-off point of  $\leq 3/5$  indicates a need to refer the patient for full evaluation of potential dementia.

As in previous articles, we use the D'Amico classification to define risk groups in localised prostate cancers [11]. We do not discuss in depth the geriatric evaluations described in previous guidelines [6–8], but we point out difficulties encountered with health status evaluation.

## 2. Evaluation of general health status

Treatment decisions in older patients with prostate cancer should not be guided by chronological age but by biological age and fitness [10] (Figs. 2 and 3). To distinguish fit from unfit patients, physicians commonly use a standard clinical assessment and Eastern Cooperative Oncology Group Performance Status (ECOG PS) [12]. Identification of fitness and estimation of risks of treatment may be improved by CGA [13]. For this reason, the SIOG strongly recommends the integration of CGA into the care plan of older patients with cancer [14].

However, the CGA of all older patients with prostate cancer may be hampered by a lack of time or trained staff, the absence of a geriatric department on site and cost. It is probably not necessary to complete a CGA in all older patients [15]. For this reason, a rational three-step model of GA has been proposed: geriatric screening of all patients to identify those who need further assessment; GA in those patients with an abnormal result on screening and geriatric interventions based on the results of the CGA. As health status changes with time and prostate cancer progression, it should be reassessed at each step of patient management.

### 2.1. Geriatric screening

A screening tool is a brief assessment conducted to help identify which patients need further evaluation by GA. In a comprehensive review of different screening tools, the G8 tool (Table 2) was the most robust [9,16]. The eight-item G8 tool was specifically developed for older patients with cancer and covers food intake, body mass index, mobility, neuropsychological problems, polypharmacy, self-perceived health status and age. The maximum score is 17, and a score of 14 or lower is considered abnormal [9]. Importantly, G8 screening is also recommended in the EAU guidelines [17].

In addition to the G8 screening, the 2017 SIOG guidelines [8] recommended screening of cognitive function by the Mini-COG™. Where the result is abnormal, there should be a full cognitive assessment of the patient's capacity to evaluate information and make informed decisions. In a meta-analysis of studies that compared the validity of ten cognitive screening tools using the Mini Mental State Examination (MMSE) as reference, [18] the Mini-COG™ most closely matched the MMSE [19]. The Mini-COG™ consists of three-word recall and a clock-drawing test and can be completed within 5 min. A cut-off point of  $\leq 3/5$  indicates a need to refer the patient for full evaluation of potential dementia (Table 3).

Table 1

Recommendations for the management of older patients with prostate cancer.

**Health status evaluation**

- Treatment should be based on health status rather than age, and also on patient preference. (Unchanged)
- The task force recommends the screening of frailty using the G8 tool and of cognitive impairment through the Mini-COG™. Patients with Mini-COG™ ≤ 3/5 require a more detailed cognitive evaluation. (Unchanged)
- In patients with G8 ≤ 14/17, evaluation of dependence, comorbidities and nutritional status are the first steps in assigning patients to one of the three health status groups: (1) 'healthy' or 'fit' patients; (2) 'vulnerable' patients and (3) 'frail' patients. Vulnerable and frail patients are candidate for geriatric assessment and geriatric interventions. (New)
- Patients benefit most from a geriatric assessment when vulnerability/frailty is detected because geriatric management will allow a more appropriate treatment plan. (Modified)

**Management of localised prostate cancer in older patients**

- Prostate cancer risk should be based on the D'Amico classification (Unchanged)
- Fit older patients with a chance of living >10 years with prostate cancer in the D'Amico high-risk group are most likely to benefit from treatment with curative intent. (Unchanged)
- Older patients with prostate cancer at D'Amico 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 at least 10 years of life expectancy. (Modified)
- The balance of benefits and harms of ADT for localised prostate cancer should be carefully assessed. Note the increased risk of diabetes, cardiovascular complications, osteoporosis, bone fractures and cognitive dysfunction. Adjuvant ADT should only be used in intermediate- and, particularly, high-risk disease. With patients who are either symptomatic or asymptomatic but at D'Amico high risk, discuss ADT monotherapy only with those unwilling or unable to receive any form of local treatment. (Modified)
- A validated tool such as the Schonberg or Lee Index can aid in predicting life expectancy independent of prostate cancer. (New)

**Management of advanced prostate cancer in older patients**

- Metastatic castration-sensitive prostate cancer
  - ADT plus 6 cycles docetaxel is a recommended first-line treatment in fit men with newly diagnosed hormone-sensitive metastatic prostate cancer. It is only appropriate in the setting of high-volume disease. Use of primary prophylaxis with G-CSF should be considered. (New)
  - ADT plus abiraterone is the other recommended first-line treatment. It is indicated in fit men with newly diagnosed hormone-sensitive metastatic prostate cancer in the setting of high-risk disease. Abiraterone use in the M1 indication should be carefully balanced against potential side-effects and costs. (New)
  - In all other cases, ADT alone remains the standard. (Unchanged)
  - Patients treated with ADT should have their bone mineral density evaluated and should receive calcium (if dietary intake is insufficient) and vitamin D supplementation. In those at high risk of low-trauma/frailty fracture, use of denosumab 60 mg subcutaneous injection every 6 months in osteoporosis prevention/treatment-approved doses is recommended. In settings where denosumab is not available, bisphosphonates in osteoporosis prevention/treatment-approved doses should be considered. Fracture risk is best assessed using a validated calculator. (Modified)
  - Prostate radiotherapy should be a standard treatment option for fit men with newly diagnosed disease with a low metastatic burden (New)
- Metastatic castration-resistant prostate cancer
  - In metastatic castration-resistant prostate cancer (mCRPC), docetaxel 75 mg/m<sup>2</sup> every 3 weeks is suitable for fit older patients. For vulnerable older patients, treatment should be guided by the results of a geriatric assessment and intervention, while the biweekly regimen should be considered in those who are unable to receive the three-weekly regimen. Use of primary prophylaxis with G-CSF should be considered with the three-weekly regimen. (New)
  - In mCRPC, abiraterone and enzalutamide are suitable first-line options. (Modified)
  - In patients who have received docetaxel, options include cabazitaxel (20 mg/m<sup>2</sup>), abiraterone and enzalutamide. (Modified)
  - 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 (although only in cases of bone metastases) should be the preferred option due to cross-resistance between androgen receptor-targeted agents. (New)
  - Careful evaluation of drug–drug interactions and proactive management of adverse events is needed in older patients. It is important to perform an initial cardiac evaluation, to treat pre-existing high blood pressure, to correct hypokalaemia and to monitor CBC, ASAT/ALAT, kalemia, glycaemia and blood pressure. Prospective evaluation of side-effects of new hormone treatment should be studied in routine clinical practice. (New)
  - Patients with bone metastases with no visceral or bulky lymph node metastases receiving first-line treatment, and after failure to docetaxel, are eligible for radium-223 (Modified)
  - Palliative treatments include radiotherapy, radiopharmaceuticals, bone-targeted therapies, palliative surgery and medical treatments for pain and other symptoms. (Unchanged)
- Early palliation should be implemented (principally in mCRPC). (Unchanged)
- Adapted physical activity is advocated at all stages of prostate cancer management; further clinical research in older patients is recommended. (New)

Table 1 (continued)

- > The management of the patient and family should include a multidisciplinary approach involving urologist, medical oncologist, radiation oncologist, geriatrician, primary care physician, nurse and palliative medicine specialist. (Modified)
- > Developing guidelines applicable in developing countries is a challenge for the future (New)

ADT, androgen deprivation therapy

## 2.2. comprehensive geriatric assessment

Patients with an abnormal G8 score ( $\leq 14/17$ ) should have a full GA. This gold standard for geriatric health status assessment [20] is a multidimensional, interdisciplinary diagnostic process to identify care needs, plan care and improve outcomes in frail older patients [21]. CGA covers several domains not covered by traditional medical assessment. These include functional status, fatigue, comorbidity, cognition, mental health status, social support, nutrition and geriatric syndromes [22]. In older patients admitted to hospital, CGA has demonstrated a beneficial effect on survival, quality of life (QoL) and rates of institutionalisation [22]. In older patients with cancer, CGA predicts survival and chemotherapy-related toxicity, identifies reversible conditions for which interventions may be needed, may influence choice of treatments and reflects patients' capacity to make decisions as well as their values and treatment goals [14].

Table 2  
G8 screening tool<sup>a</sup>.

|                                                                                                                                       |                                                  |     |
|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----|
| A - Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties? | Severe decrease in food intake                   | 0   |
|                                                                                                                                       | Moderate decrease in food intake                 | 1   |
|                                                                                                                                       | No decrease in food intake                       | 2   |
| B - Weight loss during the last 3 months?                                                                                             | Weight loss >3 kg                                | 0   |
|                                                                                                                                       | Does not know                                    | 1   |
|                                                                                                                                       | Weight loss 1–3 kg                               | 2   |
|                                                                                                                                       | No weight loss                                   | 3   |
| C - Mobility                                                                                                                          | Bed or chair bound                               | 0   |
|                                                                                                                                       | Able to get out of bed/chair but does not go out | 1   |
|                                                                                                                                       | Goes out                                         | 2   |
| D - Neuropsychological problems?                                                                                                      | Severe depression or dementia                    | 0   |
|                                                                                                                                       | Mild dementia                                    | 1   |
|                                                                                                                                       | No psychological problems                        | 2   |
| E - BMI (body mass index)? (weight in kg)/(height in m)                                                                               | BMI < 19                                         | 0   |
|                                                                                                                                       | BMI 19 to < 21                                   | 1   |
|                                                                                                                                       | BMI 21 to < 23                                   | 2   |
|                                                                                                                                       | BMI $\geq 23$                                    | 3   |
| F - Takes more than 3 prescription drugs per day?                                                                                     | Yes                                              | 0   |
|                                                                                                                                       | No                                               | 1   |
| G - In comparison with other people of the same age, how does the patient consider his/her health status?                             | Not as good                                      | 0   |
|                                                                                                                                       | Does not know                                    | 0.5 |
|                                                                                                                                       | As good                                          | 1   |
|                                                                                                                                       | Better                                           | 2   |
| H- Age                                                                                                                                | $\geq 86$                                        | 0   |
|                                                                                                                                       | 80–85                                            | 1   |
|                                                                                                                                       | <80                                              | 2   |

## 2.3. Geriatric interventions

CGA needs to be followed by interventions implemented in response to any vulnerabilities identified [23]. These interventions should be guided by a multidisciplinary team including medical specialists, nurses, psychologists, social workers, nutritionists, occupational therapists, physical therapists and pharmacists. An expert consensus algorithm for GA interventions has been published [24]. However, a prospective observational Belgian study demonstrated that only 46% of proposed interventions were actually implemented [25]. Currently, while CGA followed by interventions is recommended for all older adults with cancer, there have only been a handful of pilot interventional studies of clinical effectiveness [26–30]. Recently, a randomised controlled trial demonstrated that conducting a CGA improved communication in older patients with cancer [31]. The Clinicaltrials.gov database (accessed in April 2018) showed 145 present studies that include CGA, with many of them open to patients with any solid tumour [32]. Once completed, these studies will add to the evidence base on the effectiveness of CGA in improving clinical outcomes.

## 2.4. Future developments in health status evaluation

With the worldwide increase in the number of older people with cancer, a shortage in specialists trained in geriatrics is inevitable. Thus, there is a need for basic geriatric competency in all healthcare providers. One way to address the shortage of geriatric teams is the development of electronic assessments to assist CGA [30].

Older adults are interested in using technology to help manage their health [33–36]. The US Pew Research Center's latest data show that in 2016, 67% of Americans aged 65 years and older used the Internet. This figure ranged from 44% in those aged 80 years and older to 82% in those aged 65–69 years. Forty-two percent owned a smartphone and 32% a tablet [37].

Two recent reviews of mobile health interventions and telehealth self-management for older adults with chronic disease concluded that these approaches benefit communication, support the decision-making process and patient education and improve clinical outcomes [38,39]. The use of technology would allow older adults to complete CGAs in their home before and between appointments and thus increase their availability. Furthermore, an online CGA would allow triaging of

Table 3  
Mini-COG™ cognitive screening tool<sup>19</sup>.

| Version 1 | Version 2 | Version 3 | Version 4 | Version 5 | Version 6 |
|-----------|-----------|-----------|-----------|-----------|-----------|
| Banana    | Leader    | Village   | River     | Captain   | Daughter  |
| Sunrise   | Season    | Kitchen   | Nation    | Garden    | Heaven    |
| Chair     | Table     | Baby      | Finger    | Picture   | Mountain  |

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Step 1: three-word 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.

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 preprinted circle (see next page) for this exercise. Repeat 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-word 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  $\leq 3$  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.

older adults with complex needs to geriatric experts, so optimising scarce resources. Such an online tool could be coupled with feedback for oncology team members and patients to improve the care plan.

While two recent articles reviewed several systems for remote symptom and activity monitoring [40], fewer tools have been developed for the conduct of an online CGA [41]. To date, three online CGAs have been tested [42–44]. The first two studies included small numbers (38–100) but demonstrated high completion rates, with 51–92% of patients able to complete CGA independently. One of the two studies compared computer-based assessment with pen-and-paper measures and found both could be completed in about 15–16 min. Two-thirds of participants preferred the computer-based assessments. The third CGA tool tested is the electronic Rapid Fitness Assessment (eRFA) developed by Shahrokni *et al.* [44]. The eRFA consists of 65 items and includes a scoring algorithm. For the first 636

assessments completed, the median age was 80 years, and the median time to completion was 11 min [44]. Only 13% of patients needed help to complete the eRFA, and 90% felt it was easy to answer the questions [44]. Thus, while there is a lack of effectiveness data for these online tools, three studies suggest that they can be implemented in a busy oncology clinic. Further studies are needed to test these interventions on a larger scale to understand their clinical effectiveness and cost-effectiveness.

#### 2.4.1. Question arising from previous SIOG recommendations on health status evaluation

Health status screening as described in the 2017 SIOG prostate cancer recommendations [8] was based on the Mini-COG™ and G8 tools. Patients were divided into three health status groups based on comorbidities, functional status and nutritional status. The potential reversibility of health status impairments was taken into account in the decision-making process. Although categorising patients is difficult because there is a continuum between fit and frail, a recent study [45] demonstrated that the classification used in the 2014 guidelines was slightly (though not significantly) better in predicting one-year survival than the earlier Balducci criteria (fit-vulnerable-frail). The updated 2017 guidelines classified patients as fit, frail or disabled/with severe comorbidities, which better matches geriatric definitions.

Three questions emerge, and our discussions suggest we are still some distance from having answers: (1) is there any evidence that classifying older patients with prostate cancer is a valid means of decision-making? The answer is uncertain because we lack high-quality trials or prospective observational studies. (2) Which definition of 'frailty', and which threshold, should we use when making decisions? There is still no good, evidence-based definition. (3) What is the definition and spectrum of 'reversibility' and its impact on survival? Several studies are ongoing, but we have no evidence-based data that demonstrate effects on survival.

The recent ASCO guidelines [46] on integrating GA into daily practice with older patients receiving chemotherapy recommend use of a validated tool listed at ePrognosis [47] to estimate non-cancer-specific life expectancy, particularly in the adjuvant/curative setting. For example, the Schonberg and Lee Indices seem well validated. These indices include comorbidities but also functional status. The other recommendations are to include a screening tool (such as G8), geriatric evaluation using different screening tools and eventually the CGA [46].

In short, it is desirable to use some form of geriatric approach; to promote research on algorithms to help decision-making and on the impact of geriatric interventions on the treatment decision and to strictly

define in these patients both frailty and the reversibility of health status impairments.

The Task Force, therefore, decided to adapt the former SIOG guidelines in the light of the ASCO recommendations and to define and reword the decision-making steps:

- As a first step, older patients with prostate cancer should be screened using the G8 and Mini-COG<sup>TM</sup>.
- In the setting of early prostate cancer, we recommend use of ePrognosis [47] to estimate non-cancer-specific life expectancy and, particularly, the Schonberg and Lee Indices to aid decision-making.
- Use of a frailty index guided by GA and frameworks, where GA stratifies older patients into fit, vulnerable or frail groups, predicts mortality [46]. The SIOG Task Force decided to continue to use the 2014 categories of (1) Fit, defined by a G8 screening score of >14/17, no comorbidities, no dependence, no malnutrition and no cognitive impairment; (2) Vulnerable, where patients have either some impairment in Activities of Daily Living (ADLs) or moderate malnutrition or moderate comorbidities and (3) Frail, where older patients are either dependent on multiple ADLs or have severe malnutrition or severe comorbidities. All vulnerable and frail patients are likely to benefit from CGA and interventions.

### 3. Surgery, focal therapy and surveillance

#### 3.1. Treatment is based on risk

Treatment decisions should take into account the risk of dying from prostate cancer (i.e. tumour grade and stage), the risk of dying from another cause (i.e. comorbidities), the risks of treatment and patient preferences. In the three previous guidelines, only older patients with D'Amico high-risk prostate cancer and some selected patients with intermediate-risk prostate cancer were considered candidates for curative local treatment. Patients with low-risk prostate cancer were not.

Healthy older patients with high-risk prostate cancer are often undertreated. At the other end of the spectrum, there is concern regarding overtreatment and ensuing morbidity in low-risk patients with comorbidities and limited life expectancy. It is imperative to assess the benefit-to-risk ratio, with the latter including erectile dysfunction and incontinence.

The ProtecT study sheds light on low-risk and potentially intermediate-risk disease [48]. Patients with a screening-detected prostate cancer (60% low-risk, 40% intermediate-risk and a few high-risk) were randomised between radical prostatectomy (RP), EBRT plus six months of androgen deprivation therapy (ADT) or active monitoring. This was a 'light' active surveillance (AS) protocol with repeat biopsy at digital rectal examination (DRE)-based clinical progression or a prostate specific antigen (PSA) rise of more than 50% in 12 months.

At 10 years, there was no difference in disease-specific survival between the three arms. Although cases of metastasis were few (<10%) in all arms, the active treatment arms had a delay of disease progression and lower incidence of metastases. QoL impact was assessed using Patient-Reported Outcomes after Monitoring [49]. No overall difference in QoL was observed between the 3 modalities, while the lower frequency of specific side-effects (urinary, sexual and digestive) clearly favoured surveillance.

This trial demonstrates the harm of overtreatment, in terms of cost, and increased morbidity. This is especially so in the case of older patients with low-risk prostate cancer, and probably even in intermediate risk disease.

#### 3.2. Radical prostatectomy

Older men are more likely to be diagnosed with high-risk localised prostate cancer and may, thus, benefit more from a local treatment including RP. In high-risk disease, cancer-specific survival is up to 91% with surgery combined with adjuvant and/or salvage modalities. Survival can be up to 95% with one risk factor (ie Gleason > 7 or T > T2 or PSA > 20 ng/mL) and 79% with three [50].

Only one randomised clinical trial comparing RP to watchful waiting (WW) showed a survival benefit for those having surgery [51]. This trial was conducted before measurement of PSA was routine, with only 12% of patients being T1c and with a mean PSA level of 13 ng/mL (when reported). The updated results from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) trial with close to 20-year follow-up [52] did not show any survival benefit for RP for patients with localised low- and intermediate-risk disease, questioning the value of RP even in patients with at least 20 years of life expectancy. However, the patient selection in this trial has recently been questioned. Regarding the surgical approach, no benefit from any particular route has been observed [53].

#### 3.3. Minimally invasive therapies

Hemi-gland ablation or ablation of the index lesion(s) in older patients with prostate cancer remains experimental although promising [54]. Options include high-intensity focussed ultrasound, cryotherapy, photodynamic and laser therapy and irreversible electroporation. The only phase 3 randomised clinical trial of focal therapy used a photodynamic compound (Paderborn) and an interstitial laser to activate the product, compared to AS [55]. The major limitation of this positive trial—based on negative prostate biopsies at 24 months—is the inclusion of the lowest risk group patients in whom AS is considered standard of care in recent guidelines. Therefore, although the trial is European Medicines Agency (EMA) approved, it may be of limited value, especially as far as older adults are concerned.

### 3.4. *WW and AS*

Patients with low-risk disease are likely to benefit from WW (i.e. expectant management) or AS, with curative intervention delayed until progression. The key driver in choosing between the two approaches is individual life expectancy. An intermediate way could be active monitoring for those with only 10-year life expectancy, based on the ProtecT results, where AS might be considered overtreatment. Several guidelines now consider that AS should be standard of care for most patients with low-risk disease, and for some with intermediate-risk disease, especially if mainly based on PSA [56].

It is worth noting that many older men have lower urinary tract symptoms, often related to benign prostatic hyperplasia, that need to be clearly distinguished from a contemporaneous carcinoma. In such cases, these symptoms should be managed separately from cancer following proper recommendations.

## 4. External radiotherapy and brachytherapy

### 4.1. *Radiotherapy*

Image-guided intensity-modulated radiotherapy (IMRT) is now standard of care for localised or locally advanced prostate cancer treated with EBRT. This technique uses computer-assisted technology to modify and shape the intensity of radiotherapy beams during treatment to deliver very precise coverage of the target area. It reduces radiation exposure of surrounding normal tissues (bladder, bowel and rectum), which had previously limited the dose that could be given without unacceptable side-effects.

### 4.2. *Hypofractionation*

Hypofractionation (delivering fewer treatments at a higher dose per treatment) was well demonstrated in the Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHIP) trial comparing standard RT fractionation (37 fractions over 7.5 weeks) to 20 fractions over 4 weeks. The five-year biochemical control rate was non-inferior in the trial arm [57]. Similar results were achieved in the HYPOfractionated irradiation for PROstate cancer (HYPRO) study [58]. Further studies have demonstrated good biochemical control rates in high-risk [59], medium-risk [60] and low-risk [61] prostate cancer. However, the low-risk study reported an increase in late grade II and III genitourinary and gastroenterological toxicities [61], and the routine use of radiation in low-risk disease is not recommended.

None of these studies was tailored to the older population, although all included a proportion of patients aged

older than 70 years. Hypofractionation offers distinct advantages to both patients and radiotherapy units in reducing overall treatment time and the number of visits needed to complete therapy. Available data do not make clear whether there are any therapeutic advantages or risks specific to older patients with prostate cancer.

### 4.3. *Dose escalation with brachytherapy*

Brachytherapy also exploits the potential benefit of a smaller number of dose fractions. Ongoing trials have highlighted the role of both permanent low dose rate (LDR) and temporary high dose rate (HDR) brachytherapy, given as a 'boost' dose or alone as monotherapy.

The use of a single HDR brachytherapy boost in conjunction with EBRT is supported by a growing body of evidence and is now frequently used in both intermediate- and high-risk disease [62,63]. The ASCEND-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial compared dose escalation to 78 Gy with an LDR boost following an EBRT dose of 46Gy. The LDR boost cohort were twice as likely to be free of disease at 6.5-yr follow-up [64], although this was at the expense of increases in both clinician- and patient-reported toxicity [65,66]. The median ages were 69 years in the dose escalation and 67 years in the LDR boost arms, respectively. However, the age range in both arms extended to above 80 years, suggesting some relevance to older patients.

HDR brachytherapy as sole treatment is experimental but can be given in a single session or fractionated, with a number of lower dose insertions. A recent phase 2 study [67] of 283 men reported that a single HDR brachytherapy dose of 19–20 Gy achieves rates of late morbidity and biochemical control similar to those following 2 ( $2 \times 13\text{Gy}$ ) and 3 fractions ( $3 \times 10.5\text{Gy}$ ). Although this study does not report age-specific outcomes, a single insertion would potentially be associated with fewer toxicities, including those related to anaesthesia, which may be especially relevant in older patients. The results of further HDR brachytherapy studies are awaited.

### 4.4. *Areas of ongoing development in RT*

The ability to dose escalate or hypofractionate has clear advantages for patients, but there remains concern about increased long-term toxicity. Advances in prostate RT delivery, such as rectal spacer insertion prior to IMRT [68], demonstrate reduced post-treatment rectal toxicity. However, this study included mainly younger men (mean age 64 yrs in the spacer group). Ongoing studies are assessing the potential advantages of a rectal spacer in older patients. Dose escalation studies using stereotactic RT have yielded initially encouraging results [69], but its use remains experimental.

## 5. Medical treatment

### 5.1. Non-metastatic castration-resistant prostate cancer

Currently, two drugs are approved in this setting based on recent studies that included patients receiving ADT with a PSA doubling time of 10 months or less, a PSA value  $> 2$  ng/mL and no evidence of metastatic disease based on bone or CT scan or nodal involvement (lymph nodes with a short axis  $< 2$  cm, below the iliac bifurcation, were allowed).

In the SPARTAN trial [70], patients (median age 74 years) were randomised 2:1 to receive apalutamide, a novel competitive inhibitor of the androgen receptor, or placebo. After the first detection of distant metastasis, patients were eligible to receive treatment with abiraterone plus prednisone. The primary end-point was metastasis-free survival (MFS). The median MFS was 40.5 months in the apalutamide group vs 16.2 months with placebo ( $p < 0.001$ ). Benefit was seen in all subgroups, including patients older than 75 years. Progression-free survival (PFS), time to symptomatic progression and time to chemotherapy initiation were also longer with apalutamide. Overall survival (OS) data are not yet mature. The second PFS (on second-line treatment after apalutamide/placebo) was significantly longer in the apalutamide group than in the placebo group. Toxicity was manageable. Grade III or IV adverse events (AEs) occurred in 45.1% of patients on apalutamide and 34.2% of those on placebo. The most frequent AEs related to apalutamide were fatigue (30.4%) and rash (23.8%). Other treatment-related AEs were falls, fractures and hypothyroidism. Falls and fractures can have a major impact on the independent living of older patients. However, QoL outcomes favoured apalutamide.

In the Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer (PROSPER) trial [71], patients were randomised 2:1 to receive enzalutamide or placebo. The median age was again 74 years. Median MFS was 36.6 months in the enzalutamide group vs 14.7 months with placebo ( $p < 0.001$ ). Benefit was seen in all subgroups including older patients. Time to PSA progression and time to new antineoplastic treatment were also longer with enzalutamide. Grade III–IV AEs occurred in 31% of patients on enzalutamide and 23% on placebo. The most frequent AEs of interest on enzalutamide were hypertension (12%), cardiac events (5%) and mental impairment disorders (5%). Fatigue occurred in 33% of patients and grade III–IV fatigue in 3%. Eleven percent of patients had a fall. Enzalutamide did not lead to worsening QoL and significantly reduced the risk of clinically meaningful QoL deterioration in several Functional Assessment of Cancer Therapy-

Prostate (FACT-P) domains [72], but toxicities were not reported by the age group in this study. Data from the Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy (PREVAIL) trial show that only falls were increased in elderly patients with enzalutamide [73].

A third drug has shown in a phase III trial a benefit in the same situation [74]. Darolutamide is a novel androgen receptor antagonist that has negligible blood barrier penetration and low potential for drug–drug interaction. Patients were randomised 2:1 to darolutamide or placebo. The median age was again 74 years. Median MFS was 40.4 months in the darolutamide group vs 18.4 months with placebo ( $p < 0.001$ ). Benefit was seen in all subgroups including older patients. OS, time to pain progression, time to cytotoxic chemotherapy and time to a symptomatic skeletal were improved in the darolutamide arm. Grade III–IV AEs occurred in 24.7% of patients on darolutamide and 19.7% on placebo. Darolutamide was not associated with a higher incidence of falls, fractures, cognitive disorder or hypertension than placebo; this is of special interest in older patients. QoL was not negatively affected by darolutamide.

## 6. Newly diagnosed metastatic castration-sensitive disease

### 6.1. New hormonal treatments

In men with de novo metastatic castration-sensitive prostate cancer (mCSPC)(Table 4), two studies have demonstrated a benefit from adding abiraterone to standard ADT. The LATITUDE trial compared abiraterone 1000 mg + 5 mg prednisone + ADT to double placebo + ADT in patients with newly diagnosed metastatic prostate cancer [75,76]. The study enrolled only patients with high-risk disease, defined as having at least 2 of the following features: Gleason score  $\geq 8$ , more than 3 bone metastases and presence of measurable visceral disease. Median age was 68 years (range 33–92) with 41% of patients aged  $\geq 70$  years and 20%  $\geq 75$  years. The coprimary end-points were OS and radiological progression-free survival (rPFS). Both were met. The hazard ratio (HR) for OS was 0.62 (95% confidence interval [CI] = 0.51 to 0.76;  $p < 0.001$ ), favouring abiraterone. Median OS was 30.4 months with placebo and was not reached in the abiraterone arm. The trend for better OS was seen in all age groups:  $< 65$  (HR: 0.62);  $\geq 65$  (HR: 0.64) and  $\geq 75$  years (HR: 0.82). The trial was not powered to determine whether benefit varied by age. Toxicity was not detailed by age. Less than half of the patients in the placebo group received new hormonal agents.

Table 4  
Randomised trials in mCSPC including older patients.

| Protocol                               | CHAARTED <sup>82</sup>                                                                                                                                                                                              | STAMPEDE<br>Docetaxel <sup>80</sup>                                                                                                                                                                                                             | LATITUDE <sup>73</sup>                                                                                                                                                                      | STAMPEDE<br>Abiraterone <sup>75</sup>                                                                                                                                                                                                           |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison                             | ADT + docetaxel (6 cycles) vs ADT                                                                                                                                                                                   | ADT + docetaxel (6 cycles) vs ADT                                                                                                                                                                                                               | ADT + abiraterone vs ADT                                                                                                                                                                    | ADT + abiraterone vs ADT                                                                                                                                                                                                                        |
| Selection criteria                     | M1: 100%<br>No previous treatment: 73%<br>High-volume (65%) and low-volume (35%) disease<br>High volume defined as $\geq 4$ bone metastases with at least one beyond the spine or pelvis and/or visceral metastases | Newly diagnosed<br>M1 (59%), N+ or high-risk locally advanced ( $\geq 2$ features: T3/4, Gleason score of 8–10 and PSA $\geq 40$ ng/mL) or previously treated with radical surgery, radiotherapy or both and relapsing with high-risk features. | M1: 100%<br>Newly diagnosed<br>High risk $\geq 2$ of the following features: Gleason score $\geq 8$ , more than 3 bone metastases on the bone scan, presence of measurable visceral disease | Newly diagnosed<br>M1 (49%), N+ or high-risk locally advanced ( $\geq 2$ features: T3/4, Gleason score of 8–10 and PSA $\geq 40$ ng/mL) or previously treated with radical surgery, radiotherapy or both and relapsing with high-risk features. |
| Median age (range)                     | 64 years (36–91)                                                                                                                                                                                                    | 65 years (40–82)                                                                                                                                                                                                                                | 68 years (33–92)                                                                                                                                                                            | 67 years (39–85)                                                                                                                                                                                                                                |
| % aged $\geq 70$                       | 22%                                                                                                                                                                                                                 | 29%                                                                                                                                                                                                                                             | 41%                                                                                                                                                                                         | 37%                                                                                                                                                                                                                                             |
| % aged $\geq 75$                       | NA                                                                                                                                                                                                                  | NA                                                                                                                                                                                                                                              | 20%                                                                                                                                                                                         | NA                                                                                                                                                                                                                                              |
| Inclusion/exclusion criteria           | Adequate organ function for docetaxel                                                                                                                                                                               | Fit for chemotherapy with no clinically significant cardiovascular history                                                                                                                                                                      |                                                                                                                                                                                             | Significant cardiovascular comorbidity                                                                                                                                                                                                          |
| Impact on survival/age                 | Improved OS<br>Independent of age, in high-volume group                                                                                                                                                             | Improved OS<br>Underpowered for the older patient group                                                                                                                                                                                         | Improved OS<br>Trend in OS impact in older patients but underpowered for the older patient group                                                                                            | Improved OS<br>Underpowered for the older patient group                                                                                                                                                                                         |
| Age-stratified efficacy outcome impact | Yes                                                                                                                                                                                                                 | Yes                                                                                                                                                                                                                                             | Yes                                                                                                                                                                                         | Yes                                                                                                                                                                                                                                             |
| Impact on pain progression/age         | Delayed time to clinical progression in overall and high-volume population (impact of age unknown)                                                                                                                  | NA                                                                                                                                                                                                                                              | Delayed time to pain progression (impact of age unknown)                                                                                                                                    | NA                                                                                                                                                                                                                                              |
| Impact QoL/age                         | Decreased QoL at 3 months but nearly baseline levels by 12 months                                                                                                                                                   | NA                                                                                                                                                                                                                                              | Improved health-related quality of life (HRQoL) (impact of age unknown)                                                                                                                     | NA                                                                                                                                                                                                                                              |
| Complications                          | Neutropenic fever (6%)                                                                                                                                                                                              | Neutropenic fever (15%)                                                                                                                                                                                                                         | Hypertension (HTA), cardiovascular                                                                                                                                                          | HTA, cardiovascular                                                                                                                                                                                                                             |
| Reported age-stratified toxicity       | No                                                                                                                                                                                                                  | No                                                                                                                                                                                                                                              | No                                                                                                                                                                                          | Yes                                                                                                                                                                                                                                             |

OS, overall survival; ADT, androgen deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer.

Data from the abiraterone arm of the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial have also been published [77]. The trial had a more heterogeneous population than the LATITUDE trial because it enrolled patients with newly diagnosed metastatic or N+ prostate cancer, patients with newly diagnosed locally advanced high-risk disease (with at least 2 of the following: T3/T4, PSA  $\geq 40$  ng/mL, Gleason score  $\geq 8$ ) and patients relapsing after local treatment (M+, N+, PSA  $\geq 20$  ng/mL or PSA  $\geq 4$  ng/mL and PSA doubling time  $< 6$  months). Forty nine percent of patients had newly diagnosed metastatic disease. Median

age was 67 years (range 39–85 years). More than 37% of patients were aged  $\geq 70$  years. Patients with significant cardiovascular comorbidity were excluded. In this study, adding 1000 mg abiraterone + 5 mg prednisolone to ADT improved survival (HR = 0.63 [95% CI = 0.52 to 0.76;  $P < 0.001$ ]). In men older than 70 years, the HR for OS was 0.94 (0.69–1.29). The rate of grade III–V toxicity with abiraterone was similar in patients aged younger than 70 years vs 70 years and older (46% vs 48%).

A meta-analysis performed by the STOPCaP collaborators [78] included patients from the LATITUDE trial and those with newly diagnosed metastatic prostate

cancer from the STAMPEDE trial. Results showed a highly significant 38% reduction in the risk of death with abiraterone plus ADT that translates into a 14% absolute improvement in 3-year OS.

A further STAMPEDE study compared standard of care for metastatic prostate cancer with and without radiotherapy of the primary tumour [79]. Evidence suggests that prostate radiotherapy improves OS for men with metastatic prostate cancer who have a low metastatic burden in the prespecified subgroup analysis (HR 0.68, 95% CI 0.52–0.90;  $p < 0.007$ ), but not for unselected patients. Prostate radiotherapy should be a standard treatment option for men with newly diagnosed disease with a low metastatic burden. However data were not detailed by age groups.

## 6.2. Long-term results of chemotherapy

The most recent update [80] from the CHAARTED trial confirms the improvement in OS achieved by adding docetaxel to ADT in mCRPC: median OS 57.6 months versus 47.2 months for ADT alone (HR = 0.72; 95% CI, 0.59 to 0.89;  $p = 0.0018$ ), although the magnitude of the benefit is less than originally published, and more in line with data from the similar trials GETUG-15 [81] and STAMPEDE [82]. OS benefit was greater in ‘high-volume’ ( $\geq 4$  bone metastases with at least one beyond the spine or pelvis and/or visceral metastases) than ‘low-volume’ disease. This trend is confirmed in the aggregate analysis of GETUG 15 and CHAARTED trials [83,84]. The benefit of adding docetaxel was seen in patients both younger and older than 70 years [84]. It is noteworthy that the GETUG 15 trial [81] included only patients aged 70 years or less, although the trial was included in the combined analyses.

Several questions remain unanswered. Should every patient with mCRPC receive either abiraterone or docetaxel? Is one better than the other? If so, how should we choose between them, or should they be combined? What treatment should be given at progression? [85,86] Fortunately, there are data to shed light on these uncertainties [87].

In the STAMPEDE trial, the docetaxel and abiraterone arms recruited concurrently over a period of 17 months, during which 566 patients were enrolled [88]. An opportunistic comparison between the two arms shows no significant difference in overall or prostate cancer-specific survival. However, network meta-analysis comparing treatments for mCRPC suggests that abiraterone has the higher probability of being the more effective treatment in both OS (89–94% probability) and failure-free survival (100% probability) [89]. Whether this remains true in older patients is difficult to determine because only 29% of those enrolled were aged older than 70 years.

Further questions relevant to age concern the specific AEs associated with adding docetaxel or abiraterone in patients with heterogeneous health status. Patients in the abiraterone phase 3 trials were generally older than those in the docetaxel phase 3 trials (median age 68 vs 64 years). However, all were selected as having excellent performance status. When the three randomised trials related to ADT + docetaxel [82,84,90] are considered, the principal grade III–IV toxicities are neutropenia in 15%, febrile neutropenia (FN) in 10%, fatigue in 5% and cardiovascular events in 3%; nail changes and neuropathy were seen in  $<1\%$ . There were only five toxic deaths in a total of 1178 patients. No information is provided in older patients with mCRPC. Nevertheless, it is noteworthy that in mCRPC TAX 327, docetaxel toxicity was slightly higher in older age groups. This was particularly so for neutropenia-related outcomes in Horgan *et al.*'s [91] secondary analysis of TAX327, and the challenges in using docetaxel in the frail elderly are well recognised [92].

## 6.3. Metastatic castration-resistant prostate cancer

No new drugs have been approved for metastatic castration-resistant prostate cancer (mCRPC) since the 2017 guidelines [8]. Cabazitaxel has been approved for several years for mCRPC progressing after docetaxel. The FIRSTANA trial showed that it was not better than docetaxel in first-line treatment [93], although OS was not different, and toxicity was less when used at 20 mg/m<sup>2</sup>/cycle versus 25 mg/m<sup>2</sup>. In second-line treatment, the PROSELICA phase III non-inferiority trial compared cabazitaxel 25 mg/m<sup>2</sup> (standard dose) to a reduced dose (20 mg/m<sup>2</sup>) [94]. Cabazitaxel 20 mg was non-inferior in OS in the intent-to-treat population (primary objective). The median age of patients was 68 years, and results did not differ according to age. Grade  $\geq$ III AEs were less frequent with cabazitaxel 20 mg/m<sup>2</sup> (39.7% vs 54.5%). This reduced dose should be used in second-line chemotherapy, especially in older patients.

For patients with mCRPC, two studies of modified schedules of cabazitaxel have been published. The Spanish Oncology Genitourinary Group (SOGUG) [95] published a phase II trial of weekly cabazitaxel 10 mg/m<sup>2</sup> on days 1, 8, 15 and 22 of a 5-week cycle in seventy ‘unfit’ patients (either PS2 or previous FN with docetaxel or RT involving  $> 25\%$  of bone marrow). Patients’ median age was 74 years, 71% were PS2, 13% had experienced FN and 19% had had extensive RT. The median OS was 12.6 months (95% CI: 8.2–17.1%). The most frequent toxicities were asthenia (40%), diarrhoea (37%), anorexia (30%) nausea (27%) and peripheral neuropathy (18%). There was no FN or grade IV diarrhoea.

Clement-Zhao *et al.* [96] report on a regimen of cabazitaxel 16 mg/m<sup>2</sup> every 2 weeks with granulocyte colony stimulating factor (G-CSF) support. In their

pilot study on 43 patients, median age was 70 years and 27% were with ECOG PS  $\geq 2$ . Fourteen percent stopped treatment because of toxicity. Grade  $\geq$ III toxicity occurred in 35% of patients, with FN in 4.7%. Median OS was 15.2 months (95% CI = 9.9–19.1). Phase III trials (such as CABASTY) comparing cabazitaxel 25 mg/m<sup>2</sup> every three weeks to cabazitaxel 16 mg/m<sup>2</sup> biweekly in older patients are needed to confirm these results. Further studies of a weekly schedule are also desirable.

#### 6.4. Future developments

There are still many questions concerning the best means of treating patients with metastatic prostate cancer, particularly older patients. Nevertheless, irrespective of age and health status, abiraterone and enzalutamide should not be used consecutively because there is a high rate of cross-resistance, whereas taxanes remain active in patients pretreated with new hormonal agents.

To date, no biomarkers are ready for routine use, although there is ongoing work on circulating tumour cell (CTC) counts, CTC characterisation (AR variants, mutations), cell-free DNA and miRNA as predictors of response [97].

Increased understanding of the underlying molecular pathology, such as in DNA repair [98,99], has led to trials with targeted therapies. PARP inhibitors have shown contrasting results: olaparib showed efficacy in heavily pretreated patients, mainly in those with DNA repair alterations [99], but combining veliparib, which may be a less powerful PARP inhibitor, with abiraterone was not better than abiraterone alone [100]. In a phase II trial, olaparib in combination with abiraterone improved rPFS compared to placebo plus abiraterone in mCRPC [101]: median 13.8 vs 8.2 months; HR = 0.65 (95% CI = 0.44–0.97). Benefit seemed independent of homologous DNA repair gene status. However, the grade III toxicity rate—especially cardiovascular—was higher in the combination arm (53% vs 28%).

In relation to immunotherapy, the two trials with ipilimumab (in chemosensitive patients as monotherapy or in combination with bone-directed RT in patients previously treated with docetaxel) did not meet their primary OS end-point, although PFS was improved [102,103]. Several trials are ongoing with anti-PD-1 ligand (PD-L1)/Programmed death-1 (PD-1) monotherapy or in combination with anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA 4) antibodies, new hormonal agents or targeted therapies such as PARP inhibitors. Two phase 2 trials reported activity with anti-PD-L1 agents in enzalutamide pretreated men, probably due to the expression of PD-L1 induced by enzalutamide therapy [104]. The phase 2 trial of pembrolizumab monotherapy reported low objective response rates ( $\leq 6\%$ ) and a disease control rate of 22% in patients

with predominantly bone metastases [105]. Experience of immunotherapy in older patients with urological tumours [106] and melanoma [107] suggests that benefits in older patients are similar to those in younger patients, and—although little evidence is available—it appears that toxicity is no greater. Trials conducted specifically in older patients are needed.

#### 6.5. Radiopharmaceuticals

Radiopharmaceuticals are generally less toxic than chemotherapy and so may be especially relevant to older patients [108]. Recent analyses from the Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial of Ra-223 and from the early access programme confirm its positive impact on bone-related complications with decreased hospitalisations and an overall favourable toxicity profile even in older patients [109–111]. However, preliminary results from combination trials have shown unexpected toxicity (high rates of fractures in combination with abiraterone/prednisolone) [112]. The EMA's safety committee Pharmacovigilance Risk Assessment Committee (PRAC) has recommended restricting use to patients who have had two previous treatments for bone metastases or who cannot receive other treatments. The PRAC also confirmed its interim recommendation that Ra-223 must not be used with abiraterone acetate and prednisone/prednisolone. Ra-223 should not be used with other systemic cancer therapies, except for ADT. New radiopharmaceuticals such as 177Lu-PSMA617 [113] are in development. Phase 2 trial in older patients demonstrates clinical effect, PSA decline and few side-effects. However, phase 3 trials are needed to compare this agent against standard treatments.

### 7. Supportive care

The 2016 SIOG recommendations introduced the importance of including early supportive care and—in advanced disease—early palliative care in the management of older patients with prostate cancer [8]. This is an important part of patient management.

#### 7.1. Managing side-effects of ADT

ADT has many side-effects [114,115]. These may include myocardial infarction and cerebrovascular disease, metabolic syndrome, diabetes, obesity, dyslipidaemia, acute renal insufficiency, osteoporosis and fractures, hot flushes, sexual dysfunction, loss of libido, erectile dysfunction, cognitive impairments and gynaecomastia. The prevalence of these side-effects can be high, with obesity in 50–80% of patients, metabolic syndrome in 20–40%, osteoporosis in 25–40% and cardiovascular diseases in 15–25%. A systematic review of prevention was published in 2013 [116].

Cognitive impairment is an important concern, and a baseline cognitive evaluation may be helpful to assess any effects of ADT. A recent systematic review and meta-analysis [117] showed that ADT was not associated with overall cognitive impairment in prospective studies. There was an increased risk of any cognitive impairment in retrospective studies, but this was not significant. Thus, there is a case for further studies.

Impaired bone health is a potentially important side-effect. Recommendations for monitoring and maintaining bone health [118] include baseline bone mineral density (BMD) testing with conventional dual X-ray absorptiometry. Denosumab 60 mg subcutaneous injection every 6 months should be considered to reduce the risk of fracture in men at increased fracture risk (ideally identified with a validated tool such as the World Health Organization Fracture Risk Assessment). Bisphosphonates were effective in improving BMD, but the effect on fracture was inconclusive. However, vitamin D supplementation is recommended and, if dietary intake is low, supplementation with calcium is recommended [8].

The protective effects of exercise have been investigated [119]. Aerobic and resistance training improve cardiorespiratory fitness, muscle strength, physical function, body composition and fatigue. They may, therefore, counteract ADT-induced side-effects. Prospective randomised trials of different exercise procedures on QoL, tolerance of treatment and adherence are justified [120].

## 7.2. Managing other medical treatments in older patients

Based on models of the haematological toxicity of chemotherapy in older patients, the 2014 SIOG guidelines [7] recommended G-CSF as primary prophylaxis

[121,122]. This is compatible with current guidelines on the use of G-CSF [123]. Nevertheless, use of G-CSF should be limited to older patients receiving chemotherapy who have had in-depth evaluation of frailty, balancing the benefit and harms [124]. Otherwise, standard recommendations should be used.

The prevention of toxicities associated with new agents is an increasingly important consideration. With abiraterone in hormone-sensitive metastatic prostate cancer [75], the most frequent grade III–IV AEs were hypertension (seen in 20% of patients), hypokalemia (10%), hyperglycaemia (4%), elevated transaminases (4%) and cardiac disorders (3%), with some atrial fibrillation. In the LATITUDE trial, 20% of patients discontinued abiraterone because of side-effects (vs 12% discontinuation in the placebo arm).

In the mCRPC trial [125], the spectrum of grade III–IV toxicity showed less hypertension (1%), but the same proportion of cardiac disorders, and more frequent fluid retention (2%). However, detailed information on patients' age and comorbidity is not available. It is important to perform an initial cardiac evaluation, to treat pre-existing high blood pressure, to correct hypokalemia and to monitor complete blood count (CBC), Aspartate aminotransferase (ASAT)/Alanin aminotransferase (ALAT), hypokalemia, glycaemia and blood pressure.

With enzalutamide in mCRPC [126], the most frequent grade III side-effects were fatigue (6%) and—in around 1% of patients—diarrhoea, cardiac disorders and seizure.

With both agents, there should be further prospective study of AEs—particularly those such as fatigue and mobility with particular impact on the elderly. In the context of polypharmacy, it is important to note that

Table 5  
Estimated cancer incidence, mortality and prevalence worldwide in 2018–2040.

| Incidence (new cases)                | 2018      |           |                       | 2040     |         |           | Demographic change |                     |                      |
|--------------------------------------|-----------|-----------|-----------------------|----------|---------|-----------|--------------------|---------------------|----------------------|
|                                      | All ages  |           | All ages              | All ages |         | All ages  | Age < 70           |                     | Age ≥ 70             |
|                                      | 2018      | 2040      |                       | 2018     | 2040    |           | 2018               | 2040                |                      |
| World                                | 1,276,106 | 2,293,818 | 1,017,712<br>(+79.8%) | 650,367  | 625,739 | 963,398   | 1,330,420          | 313,031<br>(+48.1%) | 704,681<br>(+112.6%) |
| Intertropical countries <sup>a</sup> | 317,831   | 656,049   | 338,218               | 142,175  | 152,887 | 302,785   | 358,777            | 160,610             | 205,890              |
| North America & Europe <sup>b</sup>  | 585,901   | 778,661   | 192,760               | 322,806  | 263,095 | 337,783   | 440,978            | 14,977              | 177,783              |
| Mortality (cancer deaths)            |           |           |                       |          |         |           |                    |                     |                      |
| World                                | 358,989   | 737,994   | 379,005<br>(+105.6%)  | 78,844   | 284,145 | 1,129,974 | 625,020            | 38,130<br>(+50.9%)  | 340,875<br>(+120%)   |
| Intertropical countries <sup>a</sup> | 126,558   | 276,751   | 150,193               | 33,520   | 93,038  | 62,195    | 218,565            | 28,675              | 125,527              |
| North America & Europe <sup>b</sup>  | 106,317   | 191,219   | 84,902                | 15,754   | 90,563  | 16,822    | 174,396            | 1068                | 83,833               |

Modified from <sup>3</sup>: The International Agency for Research on Cancer (IARC), Globocan 2018, estimated cancer incidence, mortality and prevalence worldwide in 2018. Online analysis: prediction (Cancer tomorrow). [http://globocan.iarc.fr/Pages/burden\\_sel.aspx](http://globocan.iarc.fr/Pages/burden_sel.aspx).

<sup>a</sup> Intertropical countries were defined according to IARC regions: Eastern Africa, Middle Africa, Southern Africa, Western Africa, Caribbean, Central America, South-Eastern Asia, South-Central Asia, Melanesia, Micronesia and Polynesia. It also includes South America except Argentina, Chile and Uruguay.

<sup>b</sup> Europe, except Central and Eastern Europe.

both abiraterone and enzalutamide interact with different substrates of cytochrome P450 and have the potential for adverse interaction with many frequently used prescription and non-prescription drugs [127].

## 8. Geriatric oncology considerations in low- and middle-income countries

In developing countries, cancers tend to be diagnosed at an advanced stage, treatment is limited by resources and outcomes are generally poor. In these countries, the number of older patients with cancer will rapidly increase.

Table 5 shows that in 2040, the number of new prostate cancers in patients aged 70 years and older in intertropical countries will be the same as in countries in the North. However, the number of prostate cancer deaths will be greater in these countries due to late diagnosis and insufficient treatment.

Principles of contemporary geriatric oncology may not be easily implemented in developing countries due, principally, to a lack of geriatricians and education of health professionals.

A recent review [128] attempted to define the requirements to circumvent these difficulties. Recommendations were as follows:

- Development of adapted screening tools of frailty
- Establishment of a decision-making process to suit resources and cultures and based on standardised and simple screening tools and clinical examination
- Training of health professionals (MDs and others)
- Dissemination of scientific knowledge both in clinical and basic research.

This requires cooperation between northern/western institutions and those in other countries and a global willingness to give older adult patients with cancer in low- and middle-income countries access to adapted and active care based on efficiency and equity. Initiatives should be developed within the geriatric oncology community. Following the example of the National Comprehensive Cancer Network (NCCN) Harmonized Guidelines for Sub-Saharan Africa [129], specific guidelines on the management of prostate cancer in older patients should be developed.

## 9. Conclusion

Driven by rapid developments in the treatment of prostate cancer and in geriatric oncology, SIOG undertook to update their guidelines on managing the disease in the older patients. The Task Force continues to recommend that patients should be treated on the basis of health status evaluation and not according to chronological age. Geriatric evaluation is based on a screening test of health impairment, then evaluation of

dependence, comorbidities and nutritional status. When impairment is detected, patients may benefit from a CGA. This allows the implementation of geriatric interventions likely to facilitate a more appropriate and effective treatment plan. The Task Force recommends screening for cognitive impairment using the Mini-COG<sup>TM</sup> and the early introduction of palliative care in cases of metastatic disease.

The Task Force recommends an in-depth evaluation of health status before the start of treatment at each significant change in the disease and its management. It, therefore, regards as mandatory some form of geriatric evaluation. It also focusses on the prevention of side-effects and the potential protective role of adapted physical activity. Evaluation of the side-effects of medical treatment in everyday practice and their impact on older patients warrant further research. Major problems encountered in prostate cancer in general have recently been outlined and may help focus research adapted to older patients [130].

Finally, the Task Force recognises the potential of health status self-evaluation using new technologies and the importance of developing guidelines applicable in intertropical countries in which the majority of older patients with prostate cancer will live by the year 2040.

Task Force recommendations for the management of older patients with prostate cancer are summarised in Table 1.

## 10. Search strategy and selection criteria

Chairs of the SIOG Task Force performed searches via MEDLINE and PubMed using the terms ‘prostate cancer’, ‘neoplasms’, ‘elderly’, ‘age limit >70 years’ and ‘metastatic prostate cancer’. Articles selected were in English, focussing on the period since 01/06/2016 (the cut-off date of the literature search for the 2016 SIOG guidelines [8]) to 30/06/2018. One hundred eighty-five articles were selected based on abstract review. Section authors chose from this selection and added articles and abstracts they considered significant. Abstracts of the following meetings were also reviewed for relevant studies: EAU, ESMO, ASCO-GU and ASCO 2017 and 2018 annual meetings.

## 11. Contributors

The SIOG Board (M.A., executive secretary) had the idea and designated H.J.B. and J.-P.D. to chair the Task Force. Members were chosen by J.-P.D. and M.A. and allocated to different sections: S.O. and K.F. (France), medical oncology; N.M. (France), urology; H.P. and M.P. (United Kingdom), radiation oncology and M.P. (Canada) and L.D. (Belgium), geriatric oncology and to

the reviewing committee: E.E. (USA), medical oncology and S.A. (Canada), geriatric oncology.

The members of the writing committee developed a first draft, which was commented on by the reviewing committee and amended. Consensus was reached by the review process between July and August 2018. All authors approved the final version.

### Conflict of interest statement

H.J.B. has received travel expenses from BMS, Pfizer, Jansen, Astellas, Sanofi and Ipsen and honoraria from Sanofi, Novartis, Janssen, Ipsen and Pfizer. L.D. has received travel grants and research support from Roche, BMS, MSD and Boehringer-Ingelheim. E.E. has received grants/research support from Sanofi Janssen, Astellas and Pfizer and honoraria/advisory boards from Sanofi, Bayer, Janssen, Astellas, Takeda and Tolmar. K.F. has taken part in advisory boards and received honoraria from Amgen, Astellas, Astrazeneca, Bayer, Curevac, Essa, Genentech, Janssen, MSD, Orion and Sanofi. N.M. has received grants/research support from Takeda/Millennium, Astellas, Pierre Fabre, Sanofi and Pasteur and honoraria or consultation fees from Astellas, Janssen, BMS, Bayer, IPSEN, Ferring, Pierre Fabre, Roche, Sanofi and Steba. S.O. has received grants/research from Sanofi and Janssen and honoraria/advisory boards from Sanofi, Bayer, Janssen and Astellas. H.P. has attended and received honoraria for advisory boards, travel expenses to medical meetings and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Ipsen, Ferring, Sandoz and Novartis. M.P. has received honoraria and travel expenses from Janssen. M.A. was a consultant for Accord, Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva and Vifor, and he has received honoraria for lectures at symposia of Amgen, Bayer Schering, Biocon, Boehringer, Cephalon, Chugai, Eisai, DrReed, Genomic Health, Glenmark, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kirin Kyowa, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva and Vifor. J.-P.D. has received travel expenses from Sanofi, Janssen and Roche and honoraria from Sanofi. The other authors declare that they have no conflict of interest to disclose.

### Key messages

Individual health status, and not age, should guide management of prostate cancer in older men ( $\geq 75$  years). ‘Fit’ patients should be given the same options as younger patients; ‘vulnerable’ patients are candidates for geriatric interventions which may make it appropriate for them to receive standard treatment; ‘frail’

patients with major impairments should receive adapted or palliative treatment.

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