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

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Title: Updated recommendations of the International Society of Geriatric Oncology (SIOG) on prostate cancer management in older patients

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Abstract (299 words)

Background: The median age of prostate cancer diagnosis is 66 years, and the median age of men who die of the disease is eighty. The public health impact of prostate cancer is already substantial and, given the rapidly aging world population, can only increase. In this context, 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 EAU, ESMO, ASCO and 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 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.

Key words: prostate cancer; older patients; literature update; treatment; geriatric evaluation

Key messages:

Individual health status, and not age should guide management of prostate cancer in older men (≥ 75). “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.

6987 words

Introduction

Prostate cancer is the fourth most frequent cancer worldwide[1]. In more developed regions, the age standardized incidence per 100,000 is 68 and the age standardized mortality is 10 per 100,000[2]. Sixty percent of patients are aged 65 and older at diagnosis. This proportion will increase to 70% by 2040. Moreover, the total number of prostate cancer patients aged 70 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 and over 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 (Figure 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 paper [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 geriatrics unit.

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. 2017 also saw the dissemination within the urological community of a statement on the role of geriatric oncologists in optimizing care of urological oncology patients [10]. In this context, we can note that the EAU and SIOG are also currently co-operating on guidelines on the management of bladder cancers in older patients.

Since 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 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”. Papers selected were in English, focusing 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. 185 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. All authors approved the final version.

As in previous articles, we use the D’Amico classification to define risk groups in localized 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.

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]. 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, 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 lack of time or trained staff, the absence of a geriatrics 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 results of the CGA. As health status changes with time and prostate cancer progression, it should be reassessed at each step of patient management.

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 (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, 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 minutes. A cutoff point of $\leq 3/5$ indicates a need to refer the patient for full evaluation of potential dementia. (Table 3)

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 multi-dimensional, 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 institutionalization[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].

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 intervention studies of clinical effectiveness[26–30]. Recently, a randomized controlled trial demonstrated that conducting a CGA improved communication in older patients with cancer[31]. The Clinicaltrials.gov database (accessed April 2018) showed 145 current 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.

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 health care 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 and over used the Internet. This figure ranged from 44% in those aged 80 and over 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 older adults with complex needs to geriatric experts, so optimizing 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 to 100) but demonstrated high completion rates, with 51 to 92% of patients able to complete CGA independently. One of the two studies compared computer-based with pen and paper measures and found both could be completed in about 15-16 minutes. 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 minutes[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 and cost-effectiveness.

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 in account in the decision making process. Although categorizing patients is difficult since 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, since 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 on-going, 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 geriatrics 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™.
- 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 (ADL) or moderate malnutrition or moderate comorbidities; and 3 Frail, where older patients are either dependent in multiple ADLs or have severe malnutrition or severe comorbidities. All vulnerable and frail patients are likely to benefit from CGA and interventions.

Surgery, focal therapy and surveillance

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 and some selected intermediate-risk prostate cancer patients 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 shed light on low 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 randomized between radical prostatectomy (RP), external beam radiotherapy (EBRT) plus six months of androgen deprivation therapy (ADT), or active monitoring. This was a 'light' active surveillance protocol with repeat biopsy at DRE-based clinical progression, or a 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 (PROMs) [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 favored surveillance.

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

Radical prostatectomy (RP)

Older men are more likely to be diagnosed with high risk localized 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 randomized 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 PIVOT trial with close to 20 years follow up[52] did not show any survival benefit for RP for patients with localized 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].

Minimally invasive therapies

Hemi-gland ablation or ablation of the index lesion(s) in older patients with prostate cancer remains experimental though promising[54]. Options include high intensity focused ultrasound (HIFU), cryotherapy, photodynamic and laser therapy, and irreversible electroporation. The only phase 3 randomized clinical trial of focal therapy used a photodynamic compound (Padelipofin) and an interstitial laser to activate the product, compared to active surveillance (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 EMA-approved, it may be of limited value, especially as far as older adults are concerned.

Watchful waiting and active surveillance

Patients with low-risk disease are likely to benefit from watchful waiting (i.e. expectant management) or active surveillance, 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 years life expectancy, based on the ProtecT results, where active surveillance might be considered over-treatment. 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.

External radiotherapy and brachytherapy

Radiotherapy

Image-guided Intensity-Modulated Radiotherapy (IMRT) is now standard of care for localized 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.

Hypofractionation

Hypofractionation (delivering fewer treatments at a higher dose per treatment) was well demonstrated in the CHHIP trial comparing standard RT fractionation (37 fractions over 7.5 weeks) to 20 fractions over 4 weeks. Five year biochemical control rate was non-inferior in the trial arm[57]. Similar results were achieved in the HYPRO study[58]. Further studies have demonstrated good biochemical control rates in high[59], medium[60] and low[61] risk prostate cancer. However, the low risk study reported an increase in late Grade 2 and 3 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 over 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 prostate cancer patients.

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 external beam

radiotherapy 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 in the dose escalation and 67 in the LDR-boost arms respectively. However, the age range in both arms extended to above 80, 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 19-20Gy achieves rates of late morbidity and biochemical control similar to those following 2 (2×13Gy) and 3 fractions (3×10.5Gy). Although this study does not report age-specific outcomes, a single insertion would potentially be associated with fewer toxicities including those related to anesthesia, which may be especially relevant in older patients. The results of further HDR brachytherapy studies are awaited.

Areas of ongoing development in RT

The ability to dose escalate or hypo-fractionate 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 64yrs 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.

Medical treatment

Non metastatic castration resistant prostate cancer (M0CRPC)

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 randomized 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 endpoint 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 over 75. 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 3 or 4 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 favored apalutamide.

In the PROSPER trial[71], patients were randomized 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 3-4 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 3-4 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 FACT-P domains[72], but toxicities were not reported by age group in this study. Data from the 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 randomized 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. Overall survival, time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal were improved in the darolutamide arm. Grade 3-4 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. Quality of life was not negatively affected by darolutamide.

Newly diagnosed metastatic castration-sensitive disease (Table 4)

New hormonal treatments

In men with de novo metastatic castration-sensitive prostate cancer (mCSPC), two studies have demonstrated a benefit from adding abiraterone to standard ADT. The LATITUDE trial compared abiraterone 1,000 mg + 5mg 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 ≥ 8 , more than 3 bone metastases, presence of measurable visceral disease. Median age was 68 years (range 33 – 92) with 41% of patients aged ≥ 70 and 20% ≥ 75 . The co-primary endpoints were OS and radiological progression free survival (rPFS). Both were met. The HR for OS was 0.62 (IC 95% = 0.51 to 0.76;

$p < 0.001$) favoring 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); ≥ 65 (HR: 0.64) and ≥ 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.

Data from the abiraterone arm of the STAMPEDE trial have also been published[77]. The trial had a more heterogeneous population than LATITUDE since 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 ≥ 40 ng/mL, Gleason score ≥ 8), and patients relapsing after local treatment (M+, N+, PSA ≥ 20 ng/mL or PSA ≥ 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 ≥ 70 years old. Patients with significant cardiovascular comorbidity were excluded. In this study, adding 1,000 mg abiraterone + 5 mg prednisolone to ADT improved survival (HR=0.63 (IC 95%=0.52 to 0.76; $P < 0.001$)). In men over 70 years, the HR for OS was 0.94 (0.69 -1.29). The rate of grade 3-5 toxicity with abiraterone was similar in patients aged below 70 vs seventy and above (46% vs 48%).

A meta-analysis performed by the STOPCaP collaborators [78] included patients from LATITUDE and those with newly diagnosed metastatic prostate cancer from STAMPEDE. 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[79]. Evidence suggests that prostate radiotherapy improves OS for men with metastatic prostate cancer who have a low metastatic burden in the pre-specified 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.

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 mCSPC: median OS 57.6 months versus 47.2 months for ADT alone (HR= 0.72; 95% CI, 0.59 to 0.89; $p = .0018$), 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” (≥ 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. [83,84] The benefit of adding docetaxel was seen both in patients under and over 70 years of age[84]. It is noteworthy that GETUG 15[81] included only patients aged 70 or less, although the trial was included in the combined analyses.

Several questions remain. Should every mCSPC patient 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 mCSPC 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 since only 29% of those enrolled were aged more 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 (median age 68 vs 64 years). However, all were selected as having excellent performance status. When the three randomized trials related to ADT + docetaxel[82,84,90] are considered, the principal grade 3-4 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 mCSPC. 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 secondary analysis of TAX327[91]; and the challenges in using docetaxel in the frail elderly are well recognized[92].

Metastatic castration resistant prostate cancer (mCRPC)

No new drugs have been approved for 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[93], although OS was not different; and toxicity was less when used at 20 mg/m²/cycle versus 25 mg/m². In second line, the PROSELICA phase III non-inferiority trial compared cabazitaxel 25 mg/m² (standard dose) to a reduced dose (20 mg/m²)[94]. Cabazitaxel 20 mg was non-inferior in OS in the intent to treat population (primary objective). The median age of patients was 68, and results did not differ according to age. Grade ≥3 adverse events were less frequent with cabazitaxel 20 mg/m² (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 SOGUG[95] published a phase II trial of weekly cabazitaxel 10 mg/m² 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 4 diarrhoea.

Clement-Zhao et al[96] report on a regimen of cabazitaxel 16 mg/m² every 2 weeks with G-CSF support. In their pilot study on 43 patients, median age was 70 and 27% were ECOG PS≥2. Fourteen percent stopped treatment because of toxicity. Grade ≥3 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/m² every three weeks to cabazitaxel 16 mg/m² biweekly in older patients are needed to confirm these results. Further studies of a weekly schedule are also desirable.

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 since 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 Cells (CTC) counts, CTC characterization (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 pre-treated patients, mainly in those with DNA repair alterations[99]; but combining velaparib, 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 (IC95%=0.44-0.97). Benefit seemed independent of homologous DNA repair gene status. However, grade 3 toxicity rate – especially cardiovascular -- was higher in the combination arm (53% vs 28%).

In relation to immunotherapy, the two trials with ipilimumab (in chemo-sensitive patients as monotherapy, or in combination with bone-directed RT in patients previously treated with docetaxel) did not meet their primary OS endpoint although PFS was improved[102,103]. Several trials are ongoing with anti-PD-L1/PD-1 monotherapy or in combination with anti-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 pre-treated men, probably due to the expression of PDL1 induced by enzalutamide therapy[104]. The phase 2 trial of pembrolizumab monotherapy reported low objective response rates (≤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.

Radiopharmaceuticals

Radiopharmaceuticals are generally less toxic than chemotherapy and so may be especially relevant to older patients[108]. Recent analyses from the ALSYMPCA trial of Ra-223 and from the early access programme confirm its positive impact on bone related complications with decreased hospitalizations and an overall favorable 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 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.

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.

Managing side effects of androgen deprivation therapy

ADT has many side effects [114,115]. These may include myocardial infarction and cerebrovascular disease, metabolic syndrome, diabetes, obesity, dyslipidemia, acute renal insufficiency, osteoporosis and fractures, hot flushes, sexual dysfunction, loss of libido, erectile dysfunction, cognitive impairments, and gynecomastia. 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[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 randomized trials of different exercise procedures on QOL, tolerance of treatment and adherence are justified[120].

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 3-4 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 3-4 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, to monitor CBC, ASAT/ALAT, hypokalemia, glycaemia and blood pressure.

With enzalutamide in mCRPC[126], the most frequent grade 3 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 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].

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 and older in inter-tropical 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:

- Development of adapted screening tools of frailty
- Establishment of a decision-making process to suit resources and cultures and based on standardized and simple screening tools and clinical exam,
- 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 cancer patients 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 NCCN harmonized guidelines for Sub-Saharan Africa[129], specific guidelines on the management of prostate cancer in older patients should be developed.

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 comprehensive geriatric assessment. 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™ 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 focuses 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 recognizes the potential of health status self-evaluation using new technologies and the importance of developing guidelines applicable in inter-tropical countries in which the majority of older patients with prostate cancer will live by the year 2040.

Taskforce recommendations for the management of older patients with prostate cancer are summarized in Table 1.

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”. Papers selected were in English, focusing 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. 185 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.

Contributors

The SIOG Board (MA executive secretary) had the idea and designated HB and J-PD to chair the Task Force. Members were chosen by J-PD and MA and allocated to different sections: Stéphane Oudard and Karim Fizazi (France) medical oncology; Nicolas Mottet (France) urology; Heather Payne and Mark Prentice (United Kingdom) radiation oncology; Martine Puts (Canada) and Lore Decoster (Belgium) geriatric oncology; and to the reviewing committee: Eleni Efstathiou (USA) medical oncology and Shabbir Alibhai (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.

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Conflict of Interest statement

H Boyle has received travel expenses from BMS, Pfizer, Jansen, Astellas, Sanofi, Ipsen and honoraria from Sanofi, Novartis, Janssen, Ipsen, Pfizer.

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K Fizazi has taken part in advisory boards and received honoraria from Amgen, Astellas, AstraZeneca, Bayer, Curevac, Essa, Genentech, Janssen, MSD, Orion, Sanofi.

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S Oudard has received grants/research from Sanofi and Janssen; honoraria/advisory boards from Sanofi, Bayer, Janssen, Astellas.

H Payne 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 Prentice has received honoraria and travel expenses from Janssen.

M Puts: none

M Aapro 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, 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, Vifor

JP Droz has received travel expenses from Sanofi, Janssen and Roche; honoraria from Sanofi.

Figure legends

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

Figure 1a: Age distribution at diagnosis

Figure 1b Age distribution at death

Figure 2: Decision tree to determine patient health status [8].

Legends: mini-COG™: mini-COG™ cognitive test; ADL: Activities of Daily Living; CIRS-G: Cumulative Illness Rating Score – Geriatrics; CGA: Comprehensive Geriatric Assessment

For mini-COG™ a cutoff point of $\leq 3/5$ indicates a need to refer the patient for full evaluation of potential dementia

Figure 3: Decision making based on health status assessment [8].

Legends : G8; mini-COG™: mini-COG™ cognitive test; CGA : Comprehensive Geriatric Assessment

For mini-COG™ a cutoff point of $\leq 3/5$ indicates a need to refer the patient for full evaluation of potential dementia

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Median age at diagnosis: 66 years

Median age at death: 80 years

Screening by G8 and mini-COG TM*

**> 14/17 no
geriatric
evaluation is
needed**

**≤ 14/17 no
geriatric
evaluation is
mandatory**

- Abnormal ADL: 1 or 2
-Weight loss 5-10%
-Comorbidities CISR-G
grades 1-2

- Abnormal ADL: > 2
-Weight loss >10%
-Comorbidities CISR-G
grades 3-4

**Geriatric
assessment then
geriatric
intervention**

Group 1 FIT

**Group 2
Vulnerable**

**Group 3
Frail**

Geriatric screening with G-8 tool and mini-COG TM
Then geriatric evaluation if $G8 \leq 14/17$

Group 1
FIT

Group 2
Vulnerable

Group 3
Frail

Principles = early introduction of palliative care

Standard
treatment as
for younger
patients

Standard
treatment as
for younger
patients

Symptomatic
management
including adapted
specific treatments

Adapted physical Activity

Geriatric assessment then geriatric intervention

Table 1: Recommendations for the management of older patients with prostate cancer

<p style="text-align: center;">Health status evaluation</p> <ul style="list-style-type: none"> ➤ Treatment should be based on health status rather than age, and also on patient preference. (Unchanged) ➤ The taskforce 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 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 since geriatric management will allow a more appropriate treatment plan. (Modified)
<p style="text-align: center;">Management of localized prostate cancer in older patients</p> <ul style="list-style-type: none"> ➤ 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’ life expectancy. (Modified) ➤ The balance of benefits and harms of ADT for localized 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)
<p style="text-align: center;">Management of advanced prostate cancer in older patients</p> <ul style="list-style-type: none"> ➤ Metastatic castration sensitive prostate cancer (mCSPC) <ul style="list-style-type: none"> ○ 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 (mCRPC)

- In mCRPC, docetaxel 75 mg/m² 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/m²), 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 (though 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, 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)
- 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)

Table 2: G8 screening tool⁹

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 ≥ 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	≥ 86	0
	80 - 85	1
	< 80	2

Table 3: mini-COG™ cognitive screening tool¹⁹. Copyright S. Borson. With permission of the author (soob@uw.edu)

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.

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

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 three minutes.

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 4: Randomized trials in mCSPC including older patients.

Protocol	CHAARTED ⁸²	STAMPEDE docetaxel ⁸⁰	LATITUDE ⁷³	STAMPEDE Abiraterone ⁷⁵
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% <u>No previous treatment</u> : 73% High (65%) and low volume (35%) disease High volume defined as ≥4 bone metastases with at least one beyond the spine or pelvis and/or visceral metastases	<u>Newly diagnosed</u> M1 (59%), N+ or high-risk locally advanced (≥2 features: T3/4, Gleason score of 8–10, and PSA ≥40 ng/mL); or <u>previously treated</u> with radical surgery, radiotherapy, or both and relapsing with high-risk features.	M1: 100% Newly diagnosed High risk ≥ 2 of the following features: Gleason score ≥ 8, more than 3 bone metastases on the bone scan, presence of measurable visceral disease	<u>Newly diagnosed</u> M1 (49%), N+ or high-risk locally advanced (≥2 features: T3/4, Gleason score of 8–10, and PSA ≥40 ng/mL); or <u>previously treated</u> 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 ≥ 70 % aged ≥ 75	22% NA	29% NA	41% 20%	37% 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 independent of age, in high volume group	Improved OS Underpowered for older patients group	Improved OS Trend in OS impact in older patients but underpowered for older patients group	Improved OS Underpowered for older patients group
Age-stratified efficacy outcomes 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 HRQOL (impact of age unknown)	NA
Complications	Neutropenic fever (6%)	Neutropenic fever (15%)	HTA, cardiovascular	HTA, cardiovascular
Reported age-stratified toxicity	No	No	No	Yes

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

Incidence (new cases)									
	2018	2040	Demo-graphic change	2018		2040		Demographic change	
	All ages	All ages	All ages	Age<70	Age≥70	Age<70	Age≥70	Age<70	Age≥70
World	1,276,106	2,293,818	1,017,712 (+79.8%)	650,367	625,739	963,398	1,330,420	313,031 (+48.1%)	704,681 (+112.6%)
Inter-tropical countries*	317,831	656,049	338,218	142,175	152,887	302,785	358,777	160,610	205,890
North America & Europe**	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 (+105.6%)	78,844	284,145	1,129,974	625,020	38,130 (+50.9%)	340,875 (+120%)
Inter-tropical countries*	126,558	276,751	150,193	33,520	93,038	62,195	218,565	28,675	125,527
North America & Europe**	106,317	191,219	84,902	15,754	90,563	16,822	174,396	1,068	83,833

Modified from³: International Agency for Research on Cancer (IARC). Globocan 2018: estimated cancer incidence, mortality and prevalence worldwide in 2018. On line analysis: prediction (Cancer tomorrow). http://globocan.iarc.fr/Pages/burden_sel.aspx

*Inter-tropical 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.

** Europe, except Central and Eastern Europe.