Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology

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In 2010, the International Society of Geriatric Oncology (SIOG) developed treatment guidelines for men with prostate cancer who are older than 70 years old. In 2013, a new multidisciplinary SIOG working group was formed to update these recommendations. The consensus of the task force is that older men with prostate cancer should be managed according to their individual health status, not according to age. On the basis of a validated rapid health status screening instrument and simple assessment, the task force recommends that patients are classed into three groups for treatment: healthy or fit patients who should have the same treatment options as younger patients; vulnerable patients with reversible impairment who should receive standard treatment after medical intervention; and frail patients with non-reversible impairment who should receive adapted treatment.

Introduction

Prostate cancer is the most frequently diagnosed male cancer in both the USA[1] and Europe,[2] and one of the three most common causes of cancer-related death.[1] It is predominantly a disease of older men, with a median age at diagnosis of 66 years; 70% of deaths due to prostate cancer occur in men aged 75 years or older. The burden of the disease is expected to increase with the ageing of the population.

Available treatment guidelines make few specific recommendations for older men with prostate cancer.[3–6] In 2010, the International Society of Geriatric Oncology (SIOG) undertook a systematic bibliographical search of procedures and treatment options for localised and advanced prostate cancer to develop recommendations for the management of older men with prostate cancer.[7,8] Recommendations from the 2013 European Association of Urology (EAU) guidelines,[6] which include chapters on the treatment of prostate cancer in older men and on issues related to quality of life, accord with the 2010 SIOG guidelines.[7,8] Both highlight the under-treatment of older men, and the importance of assessing health status and comorbidities in management decisions. The recent EAU recommendations on early detection of prostate cancer specify that screening for prostate-specific antigen (PSA) should be offered to any man with a life expectancy of at least 10 years.[9]

The previously published SIOG guidelines[7,8] stated that age alone should not the provision of preclude effective treatment for prostate cancer. The aim of this report is to provide physicians with an updated comprehensive summary of evidence-based recommendations, including specific decision-making algorithms, for the management of localised and advanced prostate cancer in men older than 70 years. These care decisions should be made while taking into account patient preference.

Assessment of life expectancy, comorbidities, and health status

Although life expectancy is a major determinant of the potential benefit from therapy, it varies substantially between individuals of the same age. For example, the median life expectancy for a 75-year-old man is 8 years, but the individual's life expectancy will depend on other factors, such as comorbidities. Men in the highest quartile (likely to be healthy individuals) will live at least 14 years, whereas those in the lowest quartile (frail individuals with substantial comorbidities) will live less than 5 years (figure 1).[10] The presence of comorbidities was the strongest predictor of death (from causes other than prostate cancer)

in men with localised prostate cancer; age was a less significant predictor.[11] Health status not only affects survival; it can also affect the patient's ability to tolerate treatment-related side effects. Since 2005, the comprehensive geriatric assessment has been advocated for senior adult cancer patients (defined as patients aged 70 years or older).[12] Since the publication of the SIOG prostate cancer recommendations in this age group,[7,8] many new
screening methods have been developed to identify elderly patients with cancer who would benefit from the comprehensive geriatric assessment, including the Groningen Frailty Index,[13] the Vulnerable Elders Survey [13,14] and the G8.[15]
Screening identifies geriatric patients who should undergo an assessment of health status for comorbidities, nutritional status, and cognitive and physical functions. In a study of 1600 patients, the G8 had better predictive value than had the Vulnerable Elders Survey [13.14] The G8 screening instrument consists of eight items linked to health status domains, with a scoring system of 0–17 (table 1); a score of 14 or lower indicates impairment requiring geriatric assessment.[16] The median time for the G8 is 4 min (IQR 2–6 min). A complete geriatric assessment is then used to decide whether geriatric intervention (measures that can enhance elderly health status treatment of comorbidities, caregiver, nutrition, etc) could reverse impairment. Patients with reversible impairment (vulnerable patients) should be eligible for standard treatment, and those with irreversible impairments (frail patients) should receive adapted treatment.[7,8]

Health status domains, and reversibility of impairment

Comorbidities

Comorbidities, as measured by the Charlson index,[17] are major predictors of survival, after the exclusion of death from prostate cancer.[11] The Cumulative Illness Score Rating-Geriatrics (CISR-G) is the best available method to assess the risk of non-prostate-cancer death;[17] it rates non-lethal conditions according to their severity and potential degree of control by treatment (where grade 0 equates to no condition whereas grade 4 equates to an extremely severe condition requiring immediate treatment required, where failure to treat will result in end-organ failure or severe impairment in function).
Geriatric interventions are likely to reverse grade 2 comorbidities; grade 4 comorbidities are, by definition, irreversible.
Grade 3 comorbidities are generally irreversible, although one grade 3 comorbidity could be individually assessed for reversibility.

Dependence status

Dependence is typically assessed by use of the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)[17] scales. The ADL assesses the patient's ability to accomplish such basic activities as bathing, dressing, and feeding. The presence of one impairment (with the exception of incontinence) is classed as abnormal in older patients with prostate cancer. The IADL assesses activities that necessitate a higher degree of cognition and judgment. Four items apply to men with prostate cancer: ability to manage money, ability to manage medications, ability to use transport, and ability to use the telephone. The presence of one impairment is classed as abnormal. Geriatric intervention is likely to reverse one or two ADL impairments; the presence of more than two generally characterises irreversible dependence. Intervention is unlikely to reverse the cognitive impairments associated with abnormal IADL.

Nutritional status

Although malnutrition is associated with increased mortality in older patients,[18] unless severe, it can be reversed through geriatric intervention. Nutritional status can be estimated by using weight variation during the previous 3 months as a proxy measure.7 Good nutritional status is defined as less than 5% weight loss over 3 months; risk of malnutrition as weight loss between 5% and 10% of weight, and severe malnutrition as loss of more than 10% of weight.

Neuropsychological problems

Intervention is unlikely to reverse cognitive impairments that necessitate psychogeriatric assessment. Successful medical treatment of depression is possible.

Expert panel recommendation on screening and health status

The SIOG Prostate Cancer Working Group recommends that the decision-making process in older men with prostate cancer should be based first on systematic use of the G8 health status screening instrument. The second step should be an assessment of comorbidities (CISR-G scale), dependence status (IADL and ADL scales), nutritional status (weight loss estimation), and screening for neuropsychological problems. Finally, reversibility of specific individual impairments should be carefully checked (through medical decision making).

Older men with prostate cancer can thus be classed into three health status categories (fit, vulnerable, and frail). Healthy or fit patients are those with a G8 score of more than 14; patients are expected to tolerate any form of standard cancer treatment. Vulnerable patients are those with a G8 score of 14 or lower, and should be considered for further geriatric oncology management.[19] Patients are judged to have reversible impairment if they have any of the following: grade 2 comorbidities; one grade 3 comorbidity, which can be individually assessed for reversibility; one or two ADL impairments (apart from incontinence); risk of malnutrition reversible through geriatric intervention; and no neuropsychological problems, except depression that might be controlled with medical treatment. These patients might benefit from additional geriatric intervention and can receive standard cancer treatment after resolution of the geriatric problems.

Frail patients are those with a G8 score of 14 or less; patients are judged to have irreversible impairment if they have one or more of: several grade 3 comorbidities or a grade 4 comorbidity; more than two ADL abnormalities characterising irreversible dependence; severe malnutrition; or abnormal IADL or neuropsychological problems.

Patients in this group should benefit from geriatric intervention, and can be given specific adapted cancer treatment.

In cases of vulnerability and frailty in people, other geriatric interventions, including a comprehensive geriatric assessment, might be needed. Health status assessment and emergency geriatric interventions must be undertaken concomitantly in patients with painful metastatic prostate cancer.

Thus, groups based on health status, rather than age, should be used when making decisions about treatment options for prostate cancer (figure 2).

Treatment of prostate cancer

Background

The SIOG Prostate Cancer Working Group examined the standard approaches for the management and treatment of localised and advanced prostate cancer, and applied, when possible, evidence-based considerations specific to a senior adult population. Retrospective studies of treatment for localised prostate cancer have focused mainly on patients in good health or fitness. In trials with chemotherapeutic agents and new hormone targeted treatments that have shown the same benefit in elderly patients as in younger adult patients, the health status of the patients was either fit or was not stated.

Predictive models including age and geriatric variables

To stratify individualised risk, nomograms can be used to help decide whether the potential benefits of treatment outweigh the potential risks. O'Brien and colleagues[20] developed a nomogram for use in the preoperative setting to predict the probability of developing minimal prostate cancer on the basis of age, prostate volume, PSA concentration, and pathological features from biopsy specimens. Another nomogram[21] uses age and PSA concentration at surgery, clinical stage, and biopsy Gleason score to predict the probability of specimen confined disease (pT2–3a, R0, N0) in patients undergoing radical prostatectomy and pelvic lymphadenectomy in high-risk disease. A common feature in these nomograms is that, despite inclusion of age as a risk factor, clinical tumour characteristics have the greatest effect on patients' risk, showing that older patients have similar oncological risks to their

younger counterparts. Generally guidelines state that candidates for definitive therapy for localised prostate cancer should have a life expectancy of at least 10 years.[5,6] To standardise estimation of life expectancy, and to aid decisions on whether curative intent is viable, Walz and colleagues[22] developed a nomogram to identify individuals without sufficient life expectancy to warrant definitive treatment (radical prostatectomy or external-beam radiotherapy). Functional outcome nomograms are scarce, although Briganti and colleagues[23] have developed a preoperative risk stratification instrument that assesses the probability of recovery of erectile function after bilateral nerve-sparing radical prostatectomy. Abdollah and colleagues[24] have lately reported the first risk classification instrument to identify patients at high risk of urinary incontinence after radical prostatectomy. A nomogram calculating the risk of severe post irradiation proctitis after brachytherapy is useful to assess benefit versus injury.[25] Age seems to have a more important role in these functional outcome nomograms than in those used for treatment decisions.

Expert panel recommendations on predictive models

A model integrating several treatment options and geriatric variables (comorbidities through CISR-G, dependence, and malnutrition) is warranted for high quality individualised disease management decisions. As yet, no perfect method for this purpose is available.

Localised prostate cancer

Treatment decisions

The aim of treatment for localised prostate cancer (T1–3, N0, M0 disease) is generally curative. Treatment decisions in older men with localised prostate cancer should take into account the risk of dying from the cancer (which depends on its grade and stage), the risk of dying from another cause (which depends more on the severity of comorbidities than on age), potential treatment risks, and the patient's preferences.

Treatment decisions should also take into account the risk of developing prostate-cancer-associated complications that might interfere with existing comorbidity.

Disease progression under long-term androgen deprivation therapy can also adversely affect quality of life. For example, active treatment could be advocated in a patient with subvesical obstruction or irritative voiding, even though he would not experience a survival benefit.

A large Swedish study[26] of 117 328 patients with prostate cancer showed that mortality risk at 15 years was independent of patients' age at diagnosis but directly linked to the National Comprehensive Cancer Network (NCCN) risk groups, ranging from 10% (low risk), 20% (intermediate risk), and 35–40% (high risk). Death from causes other than prostate cancer was mainly linked to comorbidities, but the aggressiveness of prostate cancer outweighed the comorbid conditions as a risk of death for the intermediate-risk and high-risk groups.[26]

Some healthy older men with high-risk prostate cancer are undertreated; conversely, older men with low-risk prostate cancer and comorbidities, who have short life expectancy, are often over treated. Therefore, assessment of patients' oncological (eg, risk of extracapsular disease, metastases, lymph-node invasion, and cancer-specific death) and functional (eg, erectile function and continence) outcomes is important.

Radical prostatectomy

The main recommendations for radical prostatectomy are summarised in table 2. The procedure improves life expectancy in older patients with few comorbidities and intermediate or high grade disease.[28] Older men are more likely than younger patients to develop larger tumours of a higher grade,[29–32] and those with high-risk disease benefit most from radical prostatectomy.[31] Even in high-risk disease, age has a minor effect on cancer-specific mortality after radical prostatectomy (9·6% for patients aged 70 years or older *vs* 9·2% for patients younger than 70 years at 10 year follow-up).[33] Although overall mortality rates are higher in patients aged 70 years and older than in younger men, this pattern is most likely due to the higher incidence of comorbidities;[33] these findings suggest that radical prostatectomy is a viable option in healthy older men with high-risk disease and little comorbidity.

No evidence is available from randomised trials comparing radical prostatectomy with other treatment options that have curative intent. Competing risks survival analysis shows that radical prostatectomy significantly decreases risk of cancer-specific mortality in all patients with localised T1–T2 tumours (4% of patients who have undergone a radical prostatectomy die from prostate cancer *vs* 7% of those who have been treated with external-beam radiotherapy and 11% who have been observed only [p<0 · 001]), except for men aged 80 years or older in whom radiotherapy gives the best results.[34,35] Even for patients with cT3 tumours, radical prostatectomy offers 20 years of progression free survival and more than 25% of patients with cT3 tumours can be managed with surgery alone, avoiding costs and toxic effects of secondary therapies.[36] However, it is worth nothing that the quality of evidence is low.

Although 30 day mortality after radical prostatectomy increases with age, only 1% of men aged 70–79 years die during this time period.[37] Risks of death and postoperative complications after radical prostatectomy are more dependent on comorbidities than on age.[37] Conversely, the risks of long-term incontinence and erectile dysfunction after radical prostatectomy are mainly affected by increasing age. The likelihood of maintaining continence, however, is high in older patients undergoing radical prostatectomy; 86% of patients aged 70 years and older regained continence compared with 95% of patients younger than 50 years.[38]

External beam radiotherapy

The main guideline recommendations for external beam radiotherapy are summarised in table 3. Increasingly sophisticated radiotherapy techniques have allowed higher doses to be used to target the tumour while sparing normal tissue; such techniques include three dimensional conformal radiotherapy, intensity-modulated radiotherapy, and high-dose-rate brachytherapy boost, all in combination with image-guided radiotherapy. Hypofractionation is another important development. In the UK, the recommended schedule for prostate cancer radiotherapy involves 37 treatment visits. Hypofractionated regimens necessitating 19 or 20 attendances can be more convenient for older patients and have shown no additional toxicity.[39]

Combination of radiotherapy with neoadjuvant[40,41] and adjuvant androgen-deprivation therapy[42–44] improves disease-free survival at 5 years and 10 years as well as overall survival in patients with locally advanced disease (stage T3/T4), or with localised disease (stage T1/T2) and an additional high-risk factor (PSA ≥20 µg/L, Gleason grade ≥8, or both). However, the findings of D'Amico and colleagues45 suggest that only high-risk patients with no or minimal comorbidities benefit from adjuvant androgen-deprivation therapy. The toxicity of hormone therapy must be carefully monitored in men with comorbidities so that any metabolic complications can be treated early and patients can benefit from the additional survival advantage of combined modality treatments. Evidence suggests that intermediate-risk patients (stage T1/T2 with Gleason grade 7, PSA 10–20 g/L, or both) benefit from radiotherapy in combination with short-term hormone treatment.[45,46]

Brachytherapy is indicated in patients with low-risk prostate cancer (stage cT1/T2a, Gleason grade ≤6 and PSA ≤10 µg/L), prostate volume of less than 50 mL, and a good International Prostatic Symptom Score;[6] it can be a suitable option for older men with prostate cancer.

Although complications are generally less severe than are those with radiotherapy, the risks of urinary, bowel, and erectile complications increase significantly with both age and increasing severity of comorbidities, and should be taken into account when considering these therapies.[47]

Minimally invasive therapies

Focal therapy can provide a well-tolerated means of controlling cancer in older patients who haveintermediate-risk to high-risk disease with low comorbidity. The main challenge for delivering both primary and salvage focal treatment effectively is in the accurate assessment and localisation of disease judged to be clinically significant and warranting targeted treatment, both primary and salvage.

Minimally invasive, ablative technologies, such as cryotherapy and high-intensity focused ultrasound also offer primary or salvage treatment in the outpatient setting. They are also suited to deliver tissue-sparing (focal) treatment because they can selectively treat discrete volumes of prostatic tissue. Improved genitourinary functional outcomes have been shown in early studies of this focal approach with cryotherapy[48] and with high-intensity focused ultrasound.[49] Other newer techniques such as photodynamic therapy, interstitial laser, and irreversible electroporation are also being investigated as focal treatments in trials. International expert groups have made recommendations on standardised treatment and follow-up of focal therapy,[50] but it is not a standard care option at present.

Androgen-deprivation therapy

In patients with high-risk non-metastatic prostate cancer who are classed as too frail to receive curative treatment, immediate androgen-deprivation therapy had a small benefit on overall survival; however, it did not affect prostate-cancer mortality or symptom-free survival.[51] Thus, this approach can be used for patients who need symptom palliation and who are too sick or frail for curative therapy. We emphasise, however, that locally advanced disease is rarely adequately controlled in the long term by androgen-deprivation therapy alone. Furthermore, care is especially needed for older patients because androgen-deprivation therapy is associated with an increased risk of fractures,[5,52] diabetes,[53] thromboembolic events,[54] and all-cause mortality in those with history of chronic heart failure, myocardial infarction, or stroke.[55] For patients with non-metastatic prostate cancer, the evidence is that intermittent androgen-deprivation therapy is non-inferior to continuous treatment.[56]

Watchful waiting policy and active surveillance

Patients likely to benefit from watchful waiting or active surveillance (ie, delayed curative intervention on progression) have low-risk disease.[57] These patients have short expected survival, or prefer to avoid or delay the side-effects of curative therapy. Randomised studies have shown that patients who benefit more from active treatments (radiotherapy and others) than from watchful waiting have disease of intermediate or high risk, and the longest expected survival.[58] For intermediate-risk patients, the risk of dying from prostate cancer should be carefully balanced against the risk of dying from another cause.[59] Patients with a substantial risk of dying from prostate cancer need further assessment because the likelihood of an increase in stage from a clinical T1–T2 to a pathological T3–T4, or from a biopsy Gleason score of less than 7 to a pathological Gleason score of 7–10 is much higher in men aged 70 years or older than it is in younger patients.

Expert panel recommendations for localised prostate cancer

Treatment decisions should be based on health status assessment (mainly driven by the severity of associated comorbidities) rather than age, and also on the patient's preference. Fit and vulnerable senior adults in the high-risk group of the D'Amico risk classification with a chance of surviving for 10 years are likely to benefit from treatment with curative intent.[57] Older men in the low to intermediate risk group of the D'Amico risk classification are likely to benefit from an active surveillance approach or a watchful waiting policy according to their individual expected survival. The benefits and harms of androgen-deprivation therapy for localised prostate cancer should be carefully balanced in older men. Attention should be drawn to an increased risk of diabetes, cardiovascular complications, osteoporosis, and bone fractures.

Advanced prostate cancer

Androgen deprivation therapy

This approach is the mainstay of treatment for patients with metastatic prostate cancer. Castration by surgery, or through use of agonists or antagonists of luteinising hormone releasing hormone (LHRH), is the standard first-line treatment. No difference in efficacy between these treatments has been established. The standard procedure for second-line

hormonal treatment is cessation of antiandrogen therapy (if given as first-line treatment in association with an LHRH agonist). No established survival benefit has yet been shown with classic second-line and subsequent lines of hormone therapy, apart from new hormone-targeted drugs such as abiraterone acetate and enzalutamide (discussed later). When prostate cancer becomes refractory to castration, continued treatment with LHRH agonists are recommended, but no available evidence specifically supports this approach in older patients. Owing to the increased risk of osteoporosis and fracture in older men receiving androgen-deprivation therapy,[5] calcium and vitamin D supplementation should also be given, and bone mineral density should be measured at baseline. In patients at high risk of osteoporotic fracture, bone-targeted drugs such as bisphosphonates and denosumab could be helpful. The WHO Fracture Assessment instrument can be useful in to estimate risk with or without measures of bone mineral density. However, the routine use of these drugs is not recommended.[60]

Cytotoxic chemotherapy for castration-resistant prostate cancer

There is growing evidence that older age, in itself, is not a contraindication to chemotherapy. Docetaxelbased regimens for patients with castration-resistant prostate cancer improve overall survival while reducing pain and improving quality of life.[61–63] In a subgroup analysis of the TAX327 study, the survival benefit with 3-weekly docetaxel compared with mitoxantrone was similar for patients aged 68 years or younger and those older than 68 years (hazard ratios 0 · 81 *vs* 0 · 77, not significant).[62] In a retrospective analysis of patients aged 75 years or older treated with docetaxel (either 3-weekly or weekly regimen according to clinical judgment), patients with a good performance status showed responses similar to those of younger patients, and it was generally well tolerated.[64]

A phase 3 multicentre randomised study showed that a 2-weekly docetaxel regimen was associated with an increase in overall survival of 2 · 5 months, and fewer cases of grade 3–4 neutropenia compared with a 3-weekly regimen in patients with metastatic castration-resistant prostate cancer.[65]

Cabazitaxel is approved in both the USA and the EU for use in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer progressing during or after docetaxel-based treatment. In the phase 3 TROPIC study of cabazitaxel versus mitoxantrone (both with prednisone), overall survival was higher with cabazitaxel than with mitoxantrone (15 · 1 *vs* 12 · 7 months, p<0 · 0001).[66,67] The effect was not affected by age.[66,67] At 2 years, the proportion of surviving patients was twice as high with cabazitaxel than with mitoxantrone.67 Primary prophylaxis with granulocyte colony-stimulating factor significantly reduced the risk of febrile neutropenia;[68] proactive management of adverse events in high-risk patients is advocated during cabazitaxel treatment.

Several models predicting toxicity of chemotherapy in senior adults have been described lately. In the model by Hurria and colleagues,[69] factors associated with an increased risk of toxicity of grade 3 or higher included age, cancer type (gastrointestinal and genitourinary), standard chemotherapy dosing, polychemotherapy, and low haemoglobin concentration. The CRASH model was developed to predict grade 4 haematological toxicity and grade 3 or 4 non-haematological toxicity.[70] Although these two models used different criteria for predicting toxicity, geriatric, chemotherapy, and biological characteristics were predictive in both models. Severe toxicity rates were high with both models, indicating that older patients should be monitored closely.[69,70] According to Hurria and colleagues,[69] every man aged 72 years or older with prostate cancer receiving fulldose docetaxel or cabazitaxel, irrespective of any other therapy, would be in at least the medium category of risk, with an estimated risk of grade 3 or higher toxicity of 52%. If patients had aggressive disease with walking limited by pain, and slight anaemia, then they would have an estimated risk of grade 3 or higher toxicity of 83%.69 According to the CRASH model, a fit patient would have a 20–30% risk of grade 4 haematological toxicity (medium–low) and 40–60% risk of grade 3–4 nonhaematological toxicity (medium–low). A patient with worse comorbidities (eg, hypertension), and more aggressive disease, would have a 50% risk of grade 4 haematological toxicity (medium–

high), and 60% risk of grade 3–4 non-haematological toxicity (medium–high).[70] From these data, evidence to support primary prophylaxis with granulocyte colony-stimulating factor of chemotherapy in elderly patients with castration resistant prostate cancer is strong.

Hormone-targeted therapies for castration-resistant prostate cancer

Abiraterone acetate, an inhibitor of androgen biosynthesis, has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use, in combination with prednisone, in patients with metastatic castration-resistant prostate cancer. A combination of abiraterone and prednisone is effective in both chemotherapy treated and untreated patients. Overall survival was significantly longer (by 4·6 months) with abiraterone and prednisone than with placebo plus prednisone in patients previously treated with docetaxel.[71,72] In chemotherapy-naive patients with mildly symptomatic or asymptomatic metastatic castration-resistant prostate cancer and no visceral metastases, abiraterone combined with prednisone significantly improved radiographic progression-free survival, time to symptomatic progression, and time to chemotherapy use compared with placebo plus prednisone.[73] Hazard ratio analyses were in favour of abiraterone treatment in older patients in both studies.[71,72] Abiraterone is metabolised by the liver, so patients with renal impairment can receive this treatment. Abiraterone improves pain and quality of life measures[74] but use should be avoided in patients with heart failure.

Enzalutamide, an androgen receptor antagonist, improved overall survival compared with placebo in the postchemotherapy setting in patients with metastatic castration-resistant prostate cancer.[75] In patients aged 65 years and older, median overall survival was 18·4 months with enzalumatide versus 13·9 months with placebo (HR 0·63, 95% CI 0·51–0·78; p<0·001); this overall survival benefit was observed in the whole group of patients.75 Enzalumatide has therefore been approved by the FDA and the EMA. The best treatment sequence of these new drugs remains the subject of research.

Radiotherapy and radiopharmaceuticals for castration resistant prostate cancer

Radiotherapy is the first choice of treatment for localised painful metastasis in all patients with castration-resistant prostate cancer. A phase 3 study of older patients who experienced progression after docetaxel, or who were unfit for chemotherapy, compared radium-223 chloride (an α-emitting bone seeker) with placebo. Radium increased overall survival (14·0 *vs* 11·2 months, p=0·0019) and was well tolerated, with a 5-month delay to skeletal related events. On the basis of these results, radium was approved by the FDA and the EMA.[76]

Bone-targeted therapy for castration-resistant prostate cancer

Bone loss associated with androgen deprivation therapy, and the presence of bone metastases, leads to a fragile bone state, and a significant risk of skeletal-related events. In men with castration-resistant prostate cancer and bone metastases, zoledronic acid (4 mg intravenously) or denosumab (120 mg subcutaneously) every 4 weeks is recommended to prevent disease-related skeletal complications such as pathological fractures.[5,6] Men receiving zoledronic acid had fewer skeletalrelated events than had those receiving placebo (38% *vs* 49% p=0·02).[77] Denosumab treatment resulted in an 18% improvement in time to first skeletal-related event compared with zoledronic acid (p=0·001).[78] No dose modification according to renal function is needed with denosumab. However, the risk of hypocalcaemia is higher than with zoledronic acid.

Both drugs necessitate calcium and vitamin D supplementation. Good oral hygiene, baseline dental examination, and avoidance of invasive dental surgery are recommended during these treatments to reduce the risk of jaw osteonecrosis.78 Both drugs have been approved by the FDA and the EMA.

Immunotherapy for castration-resistant prostate cancer

New therapies for castration-resistant prostate cancer include sipuleucel-T, an autologous active cellular immunotherapy. It was associated with longer overall survival than placebo in patients with metastatic castration-resistant prostate cancer, although no difference in time to disease progression between groups was noted.[79] The effect did not differ between older and younger patients. The drug has been approved by the FDA and the EMA.

Expert panel recommendations for advanced prostate cancer

Androgen deprivation therapy is the first-line treatment in hormone-sensitive metastatic prostate cancer. Investigation of bone mineral status and prevention of osteoporotic fracture in high-risk patients are recommended. In metastatic castration-resistant prostate cancer, chemotherapy with docetaxel (75 mg/m2 every 3 weeks) is suitable for both fit and vulnerable older patients, and a weekly or an every-2-week regimen should be considered in frail patients. Abiraterone acetate is suitable in the first-line setting in asymptomatic or mildly symptomatic patients without visceral metastases.

New chemotherapy (cabazitaxel) and hormonal agents (abiraterone acetate and enzalutamide) are now available for second-line therapy, but careful monitoring is needed in older patients. The order in which these therapies should be given is a topic for further research. Bone targeted drugs are indicated in the prevention of bone loss, and in the treatment of patients with bone metastases. Palliative treatments include radiotherapy, radiopharmaceuticals, bone-targeted therapies, surgery, and medical treatments for pain and symptoms.

Early diagnosis of prostate cancer

The screening policy in older men with prostate cancer is controversial. Individual early diagnosis decisions should be based on the patient's health status, not on age. Two other important factors to be taken into account when screening are the increasing incidence of aggressive prostate cancer with increased age, and a patient's wish to be screened. Most guidelines do not recommend routine PSA screening in men aged 70 years or older or in any man with a life expectancy of less than 10 years.[5,6] However, life expectancy is a population estimate, and is not always individually applicable. Using the data and health status groups previously described by Walter and Covinsky,[10] we developed recommendations for giving more individualised treatment recommendations. Patients aged 70–79 years should be considered for methods that would enable early diagnosis of individualised prostate cancer. In patients aged 80–84 years, this approach should be applied to fit patients only. The decision-making procedure is described in figure 3, after selection of patients according to information obtained in figure 1, and the results of their health status assessment. The patient's age group is the first consideration: 70–79 years and 80–84 years, informed by the health status screening.

Patients should be informed about the consequences (further investigations, treatment decisions) of screening before their health status is assessed, and before every proposed diagnostic procedure. The D'Amico classification should be used to identify disease that requires curative treatment (high-risk group) or no curative treatment (low risk and intermediate-risk groups). Decision making should be mainly focused on the preferences of well-informed patients. Prospective clinical research and trials to investigate this proposed treatment model should be developed.

Conclusion

On the basis of the recommendations of the SIOG Prostate Cancer Working Group, and other international bodies, older patients with prostate cancer should be managed according to their individual health status, which is driven mainly by the severity of associated comorbid conditions, and not by patient's age. Screening for health status should include a validated screening instrument (G8), and the assessment of comorbid disorders (CISR-G scale), dependence status (IADL and ADL scales), and nutritional status (weight loss estimation). In vulnerable or frail patients, additional geriatric interventions including a geriatric assessment might be needed.

Contributors
The SIOG board (MA executive secretary) had the idea and assigned J-PD to chair the task force activity. Members of the task force were chosen by J-PD and MA. The members developed a first draft on specific topics based on former 2010 SIOG recommendations (JMF for epidemiology; J-PD, HB, LB, and MA for new validated health screening models; MK, TS, TVdB, and SJ for new predictive models in prostate cancer in elderly men; SJ, TVdB, NM, JMF, ME, and AH for prostatectomy; HP and SH for radiotherapy; ME, LD, and PC for focused treatments; NM and FS for watch and see policy; HP, SH, SO, and EE for medical treatments; J-PD and HB for new models predicting toxicity of chemotherapy; FS, SO, EE, and MA for supportive care; and NM, AH, PC, and J-PD for early diagnosis. All contributors reviewed the paper and approved the final recommendations and the final version.

Declaration of interests
J-PD has received honoraria from Novartis (conferences), from Sanofi (conferences and board meetings) and from Amgen (conferences). MA has received grants for research support from Helsinn, Merck, Perre Fabre, Sandoz, and Vifor; received honoraria and has participated in company sponsored speaker's bureaus for Amgen, Bayer Schering, BMS, Celgene, Cephalon, Chugai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, Johnson and Johnson, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Teva, and Vifor. HB has received travel grants and honoraria from Sanofi and Janssen. LD has received funding from SonaCare Medical for clinical trials, medical consultancy, and travel to conferences. ME has been a consultant to Sanofi, GSK, Advanced Medical Diagnostics, Sonatherm, and Nuada Medical. JMF received honoraria from Sanofi, Janssen, Astellas, Takeda Pharmaceuticals, and Millennium. SH has been an invited speaker at advisory boards (Sanofi, Pfizer, Janssen, AstraZeneca, Pierre Fabre, and Astellas), received conference/meeting sponsorship (Sanofi and Astellas), and research collaborations (Alliance Medical, Cancer Research UK, Ipsen, and VisionRT). MK has been a consultant for Merck and GSK. NM has received grants or research support (Takeda Pharmaceutical/Millennium, Astellas, Pierre Fabre, Sanofi, and Pasteur) and honoraria or consultation fees (Takeda Pharmaceutical/Millennium, Janssen, Astellas, BMS, IPSEN, Ferring, Novartis, Pierre Fabre, Sanofi, and AstraZeneca). SO has received honoraria from and been a consultant for Sanofi, BMS, Roche, Janssen, Bayer, and Medivation. HP has received honoraria for advisory boards, travel expenses for medical meetings, and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi, Takeda, Amgen, Ipsen, Ferring and Novartis; and her research is supported by UCLH/UCL Comprehensive Biomedical Research Centre. FS has been a consultant and received research funding from Amgen, Novartis, Astellas, Janssen, Sanofi, and Millennium. LB, PC, EE, AH, SJ, TVdB, and TS declare no competing interests. Editorial support was provided by Julie Gray and Charlotte Ball from Adelphi Communications, and funded by the SIOG.

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