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Challenges of managing elderly men with prostate cancer

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Abstract

The incidence of prostate cancer increases with age. Current evidence suggests that prostate cancer is under treated in patients aged 70 years, despite evidence of efficacy and acceptable toxicity. Radical cystectomy and definitive radiotherapy are often denied owing to fears of post-operative complications and radiotherapy-associated gastrointestinal and genitourinary toxicity. However, modern radical prostatectomy techniques provide excellent clinical outcomes with low perioperative morbidity. Moreover, volume-restricted intensity-modulated radiation therapy is a significant improvement over previous 2D conformal radiotherapy with similar efficacy and lower toxicity. Androgen-deprivation therapy is also under-prescribed among the elderly, owing to concerns of increases in cardiac deaths and osteoporosis acceleration. However, prospective trials have not identified any increase in cardiovascular mortality among elderly men receiving androgen-deprivation therapy compared to age-matched controls. Most patients on androgen deprivation eventually progress to a castration-resistant state. At this stage, the disease still responds to newer agents that target the androgen pathway and to chemotherapy. Among the elderly, chemotherapy is under-prescribed even though it has been demonstrated to be palliative and improve survival. We describe the trends in prostate cancer management in the elderly and the importance of assessing comorbidity status, tumour characteristics, and health status, including a complete geriatric evaluation, before making treatment recommendations.

Introduction

Prostate cancer is the second most common cancer diagnosed among men in the USA after non-melanomatous skin cancer.¹ This disease primarily afflicts the elderly with incidence rates increasing with age.¹ Autopsy studies suggest an increase in the age-related prevalence of incidental prostate cancer and its precursor, high-grade intraepithelial neoplasia. In a European study, the prevalence of incidental prostate cancer in men aged 30–69 was 30% and increased to 75% for those over 70 years of age.² This high prevalence of prostate cancer in the population is a key reason why the American Urological Association (AUA)

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does not recommend prostate cancer screening beyond 70 years of age (except for men in excellent health).³ It is important to distinguish morphologic prostate cancer from pathological disease, which is lethal, and avoid unnecessary screening and overtreatment.

Recent data on prostate cancer risk from the population-based Surveillance, Epidemiology, and End Results (SEER) database show that the 10-year risk of prostate cancer increases from 2.3% at age 50 years to 7.3% at age 70 years.⁴ In addition, approximately 60% of men diagnosed with prostate cancer are older than 65 years.⁴ Owing to high survival rates, many men who are diagnosed with prostate cancer at a young age may receive treatment for subsequent recurrence at an age ≥ 65 years.⁵ In general, elderly men are more likely to present with advanced-stage disease and they represent nearly 50% of the cases of metastatic disease.⁶ This Review discusses the challenges of managing prostate cancer in elderly patients, describes newer and better tolerated regimens, and focuses on the importance of personalizing therapy on the basis of comorbidities, functional status, nutritional status, disease aggressiveness and biology of the disease rather than age alone.

Defining elderly and risk stratification

A limitation in assessing the outcomes of prostate cancer treatment in the elderly is the lack of a universally accepted definition of 'elderly'. Many trials consider an age ≥ 65 years as elderly; whereas, other trials define age ≥ 70 years or ≥ 75 years as an elderly population. This is a crucial point in prostate cancer studies, as this malignancy affects mainly senior men and a consistent representation of the 'elderly' population across studies is important to enable an appropriate comparison of the outcomes. Of note, despite inconsistencies in the definition of elderly prostate cancer patients in the literature, the majority of geriatric units accept patients aged >70 years as elderly. Thus, in this Review we define 'elderly' as those patients aged >70 years.

An important factor in the decision of prostate cancer treatment is the risk stratification of patients. The risk stratification system most commonly used is the 'D'Amico risk classification'.⁷ In this system, patients are grouped into low-risk, intermediate-risk, and high-risk groups on the basis of the level of the prostate-specific antigen (PSA), of the grade (Gleason score) and clinical stage of tumour. Specifically, low-risk patients have a PSA ≤ 10 ng/ml, tumour stage $\leq$ cT2a, and Gleason score ≤ 6 . Intermediate-risk patients have a PSA in the range of 10–20 ng/ml, tumour stage is cT2b, and the Gleason score is 7. Finally, high-risk patients have PSA >20 ng/ml and/or tumour stage $\geq$ cT2c and/or Gleason score of 8–10.

Life expectancy in prostate cancer patients

A life expectancy beyond 10 years is commonly used as a criterion for offering definitive treatment to patients with localized prostate cancer, with the aim of avoiding unnecessary treatment and related adverse effects.⁸ This threshold is particularly important in light of the autopsy studies suggesting the presence of incidental prostate cancer in three quarters of elderly subjects with no known urological disease.² Assessment of life expectancy, however, was shown to be highly variable from physician to physician.⁹ According to several studies, clinicians do not rate life expectancy accurately before the initiation of a curative treatment,

and most often overestimate the time frame of residual life expectancy.^{9–11} Comorbidity indices and multivariate prognostic models along with life tables can help clinicians estimate life expectancy much better.¹² Nomograms are simple tools based on comorbidity indices, prognostic models and life expectancy tables that have been designed to assess life expectancy for patients with newly diagnosed prostate cancer. These nomograms can help therapy decision making by identifying those individuals who do not have sufficient life expectancy to warrant starting definitive prostate cancer treatment.¹³

The current practice for selecting treatments for elderly patients with newly diagnosed prostate cancer involves estimating patient survival and risk of prostate cancer-related mortality. The management of these geriatric patients focuses on preserving quality of life in addition to improving life expectancy. In fact, elderly patients with poorly differentiated cancer and a relatively long life expectancy are offered curative therapy, such as radical prostatectomy or radiation therapy. However, those patients with a life expectancy of <10 years are offered active surveillance if they have low-risk disease and androgen-deprivation therapy if they have high-risk disease.¹⁴

Radical prostatectomy

Radical prostatectomy is commonly used as the first-line curative option for localized prostate cancer. The risks of short-term treatment-related morbidity and mortality are associated with this procedure.¹⁵ Postoperative complications include bleeding, shock, renal failure, cardiac, respiratory, and vascular events.¹⁶ Rates of these complications among men aged 65–69 years and 70–74 years are similar (28% versus 31%) and increase slightly (35%, $P<0.001$) for men 75 years or older.^{17,18} However, there is an increased incidence of postoperative impotence and urinary incontinence that is particularly high in men older than 70 years (24% versus 18% for the age group 66–69 years, $P<0.001$).^{19,20} The 10-year cancer-specific survival rate after radical prostatectomy for patients aged 70 years with low-risk, intermediate-risk, and high-risk disease is 99.5%, 97.5%, and 94%, respectively.²¹ The risk of biochemical failure observed from a database of 15,899 radical prostatectomies for patients aged 70 years was 12.6% at a mean follow-up of 5.1 years.²²

Both the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines consider radical prostatectomy to be the first treatment option for candidates with a median life expectancy greater than 10 years, particularly if they have intermediate-risk or high-risk localized disease.²³ However, patient survival is affected by comorbidities, performance status, and psychosocial status, and all these factors need to be considered when estimating the life expectancy for each patient. In general, life expectancy for a 75-year-old man may vary from 5 years to 14 years, with a small minority living for much longer depending on comorbidities.²⁴ Moreover, validation studies of this median survival obtained from life charts suggest that overestimation is quite common.²⁴ In a study of 9,678 men who underwent radical prostatectomy from January 1989 to December 2000, the observed 10-year survival rate was 75.3%, whereas the predicted survival rate was 96.8%.²⁵ Overestimation was highest in the age range 65–69 years and in patients with Charlson Comorbidity Index (CCI) scores higher than 2. The CCI is a score evaluating co-occurring medical problems such as diabetes, coronary artery disease besides primary

disease. Despite this over-estimation, the majority of elderly men with localized prostate cancer in Europe and the USA do not receive curative therapy (Table 1).²⁶ In fact, an age-stratified cohort study of men with localized prostate cancer identified from the Ontario cancer registry, has reported that 14.9% of men received suboptimal treatment, and that healthy men older than aged 70 years with a Gleason scores >8 had the greatest proportion of suboptimal treatment (72.7%).²⁷ Furthermore, prostate cancer mortality was strongly related to the Gleason score in a retrospective analysis of 330 men with clinically localized disease diagnosed at age 70–74 years and managed by either surveillance or hormonal therapy for a median of 24 years; the mortality rate among these men ranged from 22% for patients with a Gleason score of <7 to 67% for those with a Gleason score of 8.²⁸ Taken together, these studies indicate that elderly patients, despite having high-risk disease accompanied by higher risk of prostate cancer-related mortality and morbidity, are more likely to be observed, rather than recommended for curative therapy, regardless of their comorbidities.²⁹ However, according to the D'Amico risk stratification system, the risk of PSA failure at 5-year for low, intermediate, and high-risk groups was 25%, 25–50%, and >50%, respectively. In all age groups, a high risk of disease was correlated with high cancer-specific mortality. In the elderly population (age 70 years), only high-risk disease was associated with significant risk of prostate cancer-specific mortality.²⁶ Thus, the increased risk of perioperative complications, a competing cause for mortality, and inherent difficulty in assessing survival and cancer-specific survival pose a unique challenge in the management of the elderly patients with prostate cancer.

New assessment tools for elderly men

The International Society of Geriatric Oncology (SIOG) convened a Prostate Cancer Working Group to define a new assessment tool that will help physicians to better evaluate each patient situation. This tool—which evaluates medical comorbidities, dependency and nutritional status—predicts whether the treatment option offered is likely to result in a survival benefit and whether the patient will be able to tolerate its associated toxicities.³⁰ This approach not only helps to identify patients unsuitable for a certain treatment, but, importantly, identifies those patients who are more likely to benefit from a specific treatment. The SIOG Working Group assessment tool classifies elderly patients as healthy, vulnerable, frail, or terminally ill.³⁰ Of note, the SIOG Working Group strongly cautions against the simple assumption that older men are likely to die of causes other than prostate cancer, because those with a high Gleason score are, in fact, more likely to die of prostate cancer.³¹ The SIOG consensus asserts that patients with high-risk disease are likely to benefit from curative treatment, whereas patients with low-risk disease and probably those with intermediate-risk disease could be managed by active surveillance.¹⁸ Patients falling in the frail and vulnerable categories require a more-comprehensive geriatric assessment, and possibly rehabilitation, before a decision is made on their fitness for aggressive treatment. Unfortunately, despite criteria available to assess the well-being of a geriatric patient, age remains the major determinant of whether a patient will receive curative treatment for prostate cancer. Hence, providers and patients need to be educated on the importance of considering the individual patient's general well-being when formulating a personalized treatment plan.

Radiotherapy

Among elderly patients with localized disease, radiotherapy is a more commonly used curative treatment as it avoids the risks associated with anaesthesia and surgery.^{29,32} Radiotherapy can be delivered via external beam or implanted brachytherapy, both of which can be administered with adjunctive androgen-deprivation therapy (ADT).³³ The use of ADT in combination with external-beam radiotherapy has become the standard of care for men receiving radiation treatment for prostate cancer.^{34,35} Despite the utility of radiotherapy as an effective and well-tolerated curative treatment, elderly patients are less likely than their younger counterparts to receive definitive radiotherapy, regardless of their risk category or comorbidity level.^{29,33} Similar to radical prostatectomy, often curative intent radiation therapy is avoided in elderly men with prostate cancer because of a perceived fear of toxicity and lack of survival benefit, although this fear is not supported by data from the literature. In an analysis of the predictors of survival among patients aged >75 years who were treated with radiotherapy, age was not found to be a predictor of overall survival when comparisons in patients aged 75–79, 80–84, or >85 years were assessed.³⁶

In a population-based study, radiotherapy improved cancer-specific mortality irrespective of the CCI among high-risk elderly patients with prostate cancer.³³ In addition, multivariate analysis confirmed the benefit of radiotherapy with significant improvement in cancer-specific mortality among the most elderly group, aged 75–80 years (HR 0.70, 95% CI 0.59–0.80; $P<0.001$). In a similar study aimed at identifying clinical factors associated with prostate cancer-specific mortality among elderly men with intermediate-risk disease treated with brachytherapy alone or in conjunction with external-beam radiotherapy, PSA rise and cardiovascular disease, but not age, were found to be predictive of prostate cancer-specific mortality.³⁷ Advanced age >70 years was also not associated with incidence of biochemical recurrence after curative radiotherapy and should not be used as an independent factor in treatment decision-making and counselling of patients with prostate cancer.³⁸

Efficacy and safety of radiotherapy in elderly

Fiorica *et al.*³⁶ evaluated the safety and efficacy of radiotherapy in a retrospective cohort study involving 107 patients aged ≥75 years with localized prostate cancer. The 5-year overall survival rate was 78% at a median follow-up of 37.8 months, and the actuarial disease-free survival at 60 months was 75.8%.³⁶ Patients with no or mild co-morbidities experienced better actuarial overall survival than those with moderate or severe co-morbidities (86.9% versus 45.3%, at 60 months). Radiotherapy was well tolerated without any significant toxicity, and no difference was detected between the different age groups (Table 1). The authors concluded that compliance with radiotherapy was good in their cohort and that the rate of toxicity was acceptable in elderly patients.³⁶

A single-centre study investigated the tolerability of 3D conformal radiation therapy in elderly patients with prostate cancer; this type of radiotherapy uses three-dimensional imaging information to focus radiation beams to the contour of the tumour to avoid irradiating surrounding organs.³⁹ Eighty patients aged >75 years were compared to 211 patients <75 years with similar comorbidities, tumour grade, and stage of disease treated at about the same time (Table 1). The researchers found that a 70 Gy dose was well-tolerated in

both groups and that there were no significant differences in the frequency of moderate-to-late adverse effects (within 30 months after finishing the therapy), which were low and ranged between 0% and 4% for the evaluated symptoms, irrespective of age group. Older patients aged >75 years in their study also had better recurrence-free survival than younger patients at 4-year follow-up (76% versus 61%, $P = 0.042$).³⁹ In general, similar adverse effects have been reported in elderly patients age >70 years and younger patients age <70 years with prostate cancer.^{40,41} The influence of patients' age on acute and chronic radiotherapy toxicity was assessed by Jani *et al.*⁴⁰ Toxicity rates were not significantly different as a function of age for either acute or late genitourinary or gastrointestinal toxicity. Villa *et al.*⁴¹ reported similar grade 1 urethra–bladder events in patients aged <80 years and patients aged >80 years. Furthermore, none of the patients aged >80 years showed genitourinary or rectal grade 2–3 acute toxicity or had to interrupt the irradiation course.⁴¹ Other studies, however, have demonstrated that advanced age is predictive of increased local adverse effects.^{42,43} Prostate cancer characteristics (involvement of apex), stage of disease, and co-morbidity (including genitourinary issues at baseline) are all factors that impact on the type and severity of adverse effects arising from radiation therapy. A single-center study of 145 patients aged ≥75 years consecutively treated with prostate brachytherapy over a period of 10 years demonstrated a 99.3% prostate cancer-specific survival and 97.1% biochemical progression-free survival at a median follow up of 5.8 years. Only one of 37 patients who died had metastatic or castration resistant prostate cancer, thus supporting use of brachytherapy in management of prostate cancer in this age group.⁴⁴

The need to stratify patients by co-morbidities rather than chronological age has been shown by D'Amico *et al.*⁴⁵ These authors investigated the effects of radiotherapy in combination with ADT for 6 months compared to radiation alone, and the interaction of comorbidities with all-cause mortality in a randomized clinical trial. In this study survival advantage was limited to intermediate-risk and high-risk patients with minimal comorbidities.⁴⁵ These results are in concordance with other studies including analyses of men with high-risk disease and minimal or no comorbidities, which have suggested benefit for aggressive radiotherapy.^{46,47}

Intensity-modulated radiotherapy in the elderly

Over the past three decades radiation therapy techniques have made significant progress with the development of three-dimensional conformal radiation therapy (CRT) and (intensity-modulated radiotherapy (IMRT)).^{48–50} IMRT is a modified form of three-dimensional CRT that restricts the volume of surrounding tissue irradiated. This technique permits delivery of a higher dose of radiation by limiting the involvement of neighbouring tissues, thereby reducing toxicity and providing cost benefits as compared to CRT.⁴⁹

In a large observational cohort study that used the SEER-Medicare database, traditional CRT ($n = 6,753$) was compared to IMRT ($n = 5,845$) in which 45% of patients in both groups were above 75 years of age; fewer composite bowel complications (2 years cumulative incidence 18.8% versus 22.4%; HR 0.86, 95% CI 0.79–0.93) and proctitis (HR 0.78, 95% CI 0.64–0.95) were noted in the IMRT-treated group.⁵¹ Several studies have established that doses >74 Gy are more effective for treatment of prostate cancer in all age groups than the

66–70 Gy dose used in the past.^{52–54} In a study involving 1,571 patients treated with radiation doses ranging from 66 to 81 Gy, higher doses of radiation (81 Gy by IMRT) were associated with increased incidence (20% versus 12% compared with lower doses of radiation) of grade 2 genitourinary and gastrointestinal toxicities at 10 years, such as rectal bleeding, mucous or pain, altered defecation frequency, as well as urinary symptoms such as urodynia, nycturia, pollakisuria, urodynia, haematuria and stenosis. However, grade 3 toxicities were infrequent (<3%) and the use of IMRT significantly reduced the risk of proctitis.⁵⁵

Androgen-deprivation therapy

Huggins and Hodges showed for the first time in 1941 that lowering testosterone levels could slow the growth of prostate cancer.⁵⁶ Since then, ADT has been the mainstay of recurrent incurable prostate cancer. The use of ADT in metastatic prostate cancer has been shown to reduce PSA levels, delay disease progression, and produce objective anti-tumour responses.⁵⁷

Currently, the primary approach to treat patients with recurrent and/or metastatic prostate cancer involves lowering the testosterone levels to castration levels.⁵⁷ This can be achieved surgically by bilateral orchiectomy or medically by administration of drugs. There are two drug-based methods for androgen deprivation. One prevents the pituitary gland from releasing LH by using gonadotropin-releasing hormone (GnRH or LHRH) modulators (agonists or antagonists), thus preventing stimulation of testosterone production, and the other one blocks the body's ability to use androgens by using androgen-blockers. However, the administration of GnRH or LHRH agonists (such as leuprorelin, goserelin, triptorelin) or antagonists (degarelix) can be used also in combination with androgen receptor inhibitors.⁵⁷ Specifically, an androgen receptor blocker is used for 1 week before and continued for an additional 1–2 weeks after the administration of GnRH agonist to ameliorate the effects of the transient rise in testosterone (testosterone flare) during initiation of therapy with this agent. The decision to undergo surgical or medical orchiectomy is based on a number of factors, including patient preference, co-morbidity status, cost, and treatment availability.⁵⁷ The objective of medical therapy is to achieve testosterone levels similar to surgical castration; recently, several experts agreed on a consensus level of serum testosterone <20 ng/dl.^{58,59} Surgical orchiectomy is still the preferred choice in many countries because it is inexpensive and leads to a rapid reduction of testosterone in a short time (less than 12 h); however, this approach has largely been replaced by medical orchiectomy in North America and Europe, at least in part because of the huge psychological effect associated with castration.^{60,61}

Adverse effects of ADT in the elderly

Despite benefits of ADT, it is important to recognize the metabolic alterations and adverse effects of androgen suppression in other organ systems (otherwise referred to as androgen-deprivation syndrome).^{62,63} Androgen suppression has long been associated with numerous adverse effects that markedly diminish quality of life, such as hot flushes, decreased libido, and mood changes. Furthermore, ADT is also associated with new onset or progression of

diabetes, hyperlipidaemia, metabolic syndrome, osteoporosis, fractures, and increased risk of cardiovascular events.^{57,64}

The 5-year cumulative incidence of death from cardiovascular causes in patients >65 years of age treated with ADT for localized prostate cancer was 5.5%, compared to 2% without ADT, although this difference did not attain statistical significance.⁶⁵ Of note, older patients aged 75–84 years with low-to-moderate grade tumours and stage T1–T3 have a higher risk of dying from cardiovascular disease than prostate cancer.⁶⁶ The association of ADT with cardiovascular disease, myocardial infarction, and diabetes, while seen in some studies, has not been uniformly seen in larger trials.^{67–71} Longstanding androgen ablation leads to osteopenia (often managed with calcium and vitamin D supplementation) or even osteoporosis, for which bisphosphonates are recommended.^{64,72} Administration of denosumab and zoledronic acid decrease the rates of skeletal-related events (pathological fractures, bone pain, need for radiation or surgery for bone metastasis or spinal cord compression) and is recommended in the case of skeletal metastasis.^{73,74} In patients with non-metastatic castration-resistant prostate cancer (CRPC) and with PSA doubling times of less than 6 months, treatment with denosumab delayed the occurrence of bone metastasis by 7.2 months (HR 0.77; $P = 0.006$).⁷⁵

Importantly, many of these adverse events occur at a greater frequency in the elderly, as they have increased likelihood of co-morbidities. Therefore, practitioners treating patients with prostate cancer should also evaluate for all patients the ‘geriatric’ outcomes, including functional losses, cognitive impairment, and falls.^{76,77} The optimal timing for initiation of ADT is not well established and has to be individualized particularly in the elderly.⁷⁸ A review of randomized trials suggests that early ADT treatment decreases prostate cancer mortality without any improvement in overall survival.⁷⁹ Another treatment strategy for elderly patients with prostate cancer has been intermittent androgen ablation as opposed to continuous therapy, with the hope of delaying androgen resistance and thereby prolonging survival and improving quality of life.⁸⁰ The NCIC clinical trials group led a phase III clinical trial enrolling 1,386 patients who had PSA progression alone after definitive radiation therapy and randomized them to receive either androgen ablation with LHRH agonist intermittently in 8-month cycles with set triggers for restarting therapy or continuous therapy.⁸¹ After a median follow-up of 6.9 years, intermittent therapy led to improvement in some quality-of-life factors (hot flashes, sexual desire and urinary symptoms) and was non-inferior to continuous therapy with respect to overall survival (8.8 years versus 9.1 years in continuous arm; HR 1.02, 95% CI 0.86–1.21). In a similar large phase III study in previously untreated men with known metastatic disease, intermittent therapy was non-inferior to continuous therapy, although there was a trend towards inferior survival (5.1 years versus 5.8 years in continuous therapy group; HR 1.10, 90% CI 0.99–1.23).⁸²

Androgens receptor blockers

Androgens receptor blockers (ARB)—which include flutamide, nilutamide, bicalutamide, and enzalutamide—competitively inhibit the binding of testosterone to its receptors. ARBs are seldom indicated as monotherapy in advanced-stage prostate cancer because of poorer efficacy as compared to medical or surgical castration.⁸³ However, ARBs can be initiated in

combination with chemical or surgical castration for complete andro-gen blockade either at the start of therapy or at disease progression. The phase III AFFIRM trial assessing the effect of the newer ARB, enzalutamide, in patients with CRPC following disease progression on chemotherapy with docetaxel, found a similar improvement in overall survival, progression- free survival, and reduction in PSA levels in patients aged >75 years compared to patients aged <75 years (Table 1).^{84,85} In the phase III PREVAIL trial, treatment with enzalutamide in chemotherapy-naive patients with metastatic CRPC led to improvement in overall survival (HR 0.7; $P<0.0001$) and recurrence-free survival (HR 0.19; $P<0.0001$) as compared to placebo.⁸⁶

Androgen synthesis inhibitors

Ketoconazole blocks androgen synthesis by inhibiting the steroid 17- α -hydroxylase and 17,20 lyase enzyme in the androgen synthesis pathway, and this agent has established activity in CRPC.⁸⁷ In a phase III study involving 260 patients with CRPC with disease progression following ARB therapy, ketoconazole demonstrated a >50% reduction in PSA in 27% of patients compared with an 11% reduction seen with withdrawal of ARB ($P=0.0002$); however, ketoconazole failed to show improvement in overall survival.⁸⁷ Furthermore, keto-conazole reduced androgen levels only temporarily, as these levels rose at the time of disease progression, which led to resistance.⁸⁷ Abiraterone acetate is a more selective and potent inhibitor of steroid 17- α -hydroxylase and C17,20-lyase activities. In a large phase III study (COU-AA-301) involving 1,195 patients who had previously received docetaxel therapy, treatment with abiraterone acetate led to improvement in survival from 10.9 months in the placebo group to 14.8 months in treatment group (HR 0.65; $P<0.001$).⁸⁸ In a similar phase III study (COU-AA-302) in chemotherapy-naive patients, treatment with abiraterone acetate led to improved radio-graphic progression-free survival compared to placebo (16.5 months versus 8.3 months; HR 0.53; $P<0.001$), and the trial was unblinded at the planned interim analysis.⁸⁹ Treatment with abiraterone acetate was well tolerated and resulted only in a small increase in adverse events associated with mineralocorticoid excess (55% versus 43%), which mostly consisted of grade I or II fluid retention and hypokalemia.⁸⁹ In both studies, subgroups of patients aged ≥ 65 years and patients aged ≥ 75 years seemed to gain similar benefit from abiraterone acetate therapy as compared to the placebo arms.⁸⁹

Cytotoxic chemotherapy in elderly patients

An age-biased tendency to deny best available therapy to otherwise fit elderly patients is well documented in studies involving not only patients with prostate cancer, but also those treated for breast cancer and colon cancer.^{90–93} The use of chemotherapy for elderly patients with advanced-stage disease is less compared to the younger population, although there is an increase in incidence of prostate cancer with age. A study assessing physician attitudes towards the use of cytotoxic chemotherapy in elderly patients with advanced-stage prostate cancer found a low prescription of chemotherapy even among fit elderly patients.⁹³ Overall, medical oncologists and urologists are concerned about the toxicity of chemotherapy, the perceived lack of benefit, the negative effect on quality of life, and patient refusal to consider such a treatment option.^{92,93} However, the major factor contributing to the underutilization of chemotherapy in elderly is fear of toxicity due to age-related changes in pharmacokinetics

and pharmacodynamics of chemotherapeutic drugs.⁹⁴ A pooled analysis of two phase II trials of weekly docetaxel in men with metastatic CRPC showed that similar grade 3–4 adverse events were observed in patients aged >70 years compared to younger patients.⁹⁵

In a study of 195 patients aged >70 years evaluating the acceptance of chemotherapy in elderly patients, an overwhelming majority of patients were found willing to consider chemotherapy as a treatment option.⁹⁶ Overall, 70.5% of American and 77.8% of French elderly patients with cancer were willing to accept an intense chemotherapy regimen (platinum with a taxane-type regimen) despite severe toxicity, while acceptance for milder regimens was 88.5% in American and 100% in French patients. These data clearly challenge perception about poor acceptance of chemotherapy among elderly patients.

In retrospective analyses of 1,194 men with CRPC enrolled in eight multi-institutional phase II and III chemotherapy/hormonal therapy trials performed by the Cancer and Leukemia Group B (CALGB), clinical outcomes were assessed by age.⁹⁷ The findings of this study supported the hypothesis that older men have a worse prognosis and clinical outcomes. Men between 80–89 years of age were at 34% increased relative risk of prostate cancer-related death as compared to men aged 70–79 years. Surprisingly, men who were between 50–59 years of age had a 26% increased risk for prostate cancer-related death and a 25% increased risk for clinical progression as compared to men aged 70–79 years. The two higher risk age groups of men aged 50–59 and 80–89 years had lower incidence of prostatectomy and prior radiation as compared to men aged 60–69 years and 70–79 years. Patients aged 50–59 years had a higher Gleason score compared to other groups, while those aged 80–89 years had high-risk characteristics of lower haemoglobin, higher PSA and lactate dehydrogenase (LDH), thus explaining the cause for higher mortality in these cohorts.⁹⁷

A dataset derived from six CALGB studies was used to develop a prognostic model for predicting survival in men with metastatic CRPC.⁹⁸ The proportional hazards model was used to develop a multivariable model considering pretreatment factors and to construct a prognostic model. The median age in the training data set was used as a dichotomous variable—less than or more than 71 years for this study. Performance status, Gleason score, LDH, PSA, and alkaline phosphatase were all significant factors predicting survival in men with metastatic CRPC; however, age was not a factor.⁹⁸ This result is not surprising because in the previous analysis age was found to be a bimodal risk factor, with 50–59 years and 80–89 years representing the highest risk groups. Another study involving 333 patients with CRPC found a lower median survival for patients diagnosed with prostate cancer either before 55 or after 75 years of age as compared to the two other groups of patients aged 55–64 and 65–74 years.⁹⁹

In the seminal TAX 327 study (a randomized, non-blinded, phase III trial), 1,006 patients with CRPC received also prednisone twice daily were randomly assigned to receive docetaxel weekly or every 3 weeks or mitoxantrone every 3 weeks.¹⁰⁰ Docetaxel administered every 3 weeks with prednisone led to improved pain palliation, greater PSA response, improved quality of life and overall survival as compared to similar timeline treatment with mitoxantrone plus prednisone.¹⁰⁰ An updated survival analysis of the TAX 327 study, performed in March 2007 after 867 deaths, showed similar survival benefits in

patients younger or older than 68 years.¹⁰¹ The hazard ratio (HR) for death of younger and older patients was 0.81 and 0.77, respectively, for docetaxel every 3 weeks compared with mitoxantrone. Similar benefit was found at a more extreme age cut off of 75 years (HR = 0.80).¹⁰¹ In a study of 175 patients aged ≥75 years treated with docetaxel at tertiary care centres in France, median overall survival and adverse events correlated with performance status and presence of visceral disease, but not with age.¹⁰² Patients aged ≥75 years had similar incidence of grade 3–4 adverse events as compared to men aged ≥74 years in the TAX327 study (Table 1).¹⁰²

The effect of age (greater than or less than 70 years) on safety and efficacy of the weekly treatment with docetaxel was analysed in a pooled analysis of two phase II trials in men with metastatic CRPC.⁹⁵ Despite having higher risk features of lower haemoglobin and higher PSA at baseline in the cohort of older patients (age >70 years), PSA response, measurable disease response rate, time to progression, and survival were not affected by age in either univariate or multivariate analyses.⁹⁵ These findings are consistent with previous studies showing that docetaxel chemotherapy in patients with CRPC is equally well tolerated and effective in the elderly patient population.

Cabazitaxel is a semi-synthetic derivative of the natural taxoid 10-deacetylbaaccatin III that is efficacious in docetaxel-resistant patients.¹⁰³ A study assessing the tolerability of cabazitaxel in elderly patients (age >70 years; *n* = 325 as compared to age <70 years; *n* = 421) showed that treatment-related adverse effects were similar in the two groups and were manageable in the elderly with metastatic CRPC.¹⁰⁴ Elderly patients (aged >70 years) had similar rates of toxicity when compared to patients aged <70 years, including delayed treatment due to cabazitaxel-related adverse events (10.6% versus 14.7% for age <70), dose reductions (16% versus 18.5%), and febrile neutropenia (5.5% versus 5.2%).¹⁰⁴

Furthermore, correlation between comorbidities and toxicity was assessed for patients aged >65 years who were treated with cabazitaxel after a docetaxel-based therapy. The presence of comorbidities did not interfere with the toxicity of cabazitaxel, thus supporting its efficacy and safety in older patients unresponsive to previous docetaxel therapy.¹⁰⁴

Cabazitaxel is being studied in a randomized phase III trial¹⁰⁴ as frontline therapy among chemotherapy-naïve patients compared with docetaxel and among elderly patients over 75 years of age.¹⁰⁵ These studies clearly suggest that both docetaxel and cabazitaxel are well tolerated and effective in healthy elderly patients with CRPC. Thus, the use of chemotherapy in elderly men should be directed by the analysis of functional status, co-morbidities, and a comprehensive geriatric assessment.

Immunotherapy

The development of immunotherapies for cancer is particularly attractive because of their relatively low toxicity and their potential to be effective across tumour types. Advances in prostate cancer immunology led to development of sipuleucel-T, a dendritic cell vaccine, the first immunotherapy for treating CRPC and the first vaccine ever to be approved by the US FDA for management of any cancer.¹⁰⁶ Sipuleucel-T therapy involves *ex-vivo* sensitization of antigen-presenting cells (APC) to the chimeric antigen PA2024, a custom-fusion protein combining tumour-associated antigen prostatic acid phosphatase to an immune adjuvant,

granulocyte-macrophage colony-stimulating factor (GM-CSF).¹⁰⁷ These activated APCs are infused back in to the patient and stimulate a T-cell response against prostatic acid phosphatase expressed on prostate cancers cells. In a multicentre randomized trial, 512 patients with meta-static CRPC and minimally symptomatic or asymptomatic disease were treated with sipuleucel-T or placebo. Treatment with sipuleucel-T was very well tolerated and treatment was associated with a 4.1 month improvement in overall survival compared with the placebo arm.¹⁰⁸ There was no PSA response (reduction in PSA 30% or delay in PSA progression) or radiographic response in the treatment group compared with the placebo group.¹⁰⁸ Of note, separation of survival curves between sipuleucel- T and control arms at 6 months after the initiation of the treatment was observed in this and other similar phase III trials, suggesting a possible delayed clinical effect for this immunotherapy.¹⁰⁹ Despite concerns for immune-senescence in the elderly, subgroup analysis of patients older than the median age of 72 years showed improvement in overall survival favouring sipuleucel-T therapy, while the benefit among patients younger than 72 years was less clear.¹⁰⁸ Immunotherapy with sipuleucel- T is very well tolerated and grade 3 side effects are rare compared with placebo. A post- marketing surveillance study has been completed to assess any increase risk of cerebro-vascular events and other adverse effects with this therapy. Immunotherapy with sipuleucel-T and other vaccines in development offer a unique therapeutic modality that is remarkably well tolerated and has a potential for durable response without interfering with administration of subsequent therapies.^{108,110} However, occurrence of disease progression before clinical antitumour response to immunotherapies, leaves them without any objective measure of response, despite consistent improvement in survival demonstrated across clinical trials.^{108,111}

Radionuclide—radium-223

Bone metastasis is a major cause of morbidity leading to pain, pathological fractures, spinal cord compression and decreased mobility in patients with prostate cancer and afflicts over 90% of patients with advanced disease.^{100,103,108,112} Radium-223 dichloride is a novel alpha-emitting calcium mimetic radioisotope that selectively targets and binds to sites of bone metastasis emitting high energy over a radius of a few cells depth.^{113,114} An alpha particle comprises two protons and two neutrons and has several orders of magnitude larger mass compared with beta emission. Alpha particles have a short path length of <100 µm along which they deposit this energy (that is, a high linear energy transfer), which is highly lethal and requires a small fraction to kill cells as compared to the low energy beta emitters.¹¹⁵ In the phase III ALSYMPCA trial, 921 patients with CRPC and symptomatic bone metastasis were randomly assigned in a 2:1 fashion to treatment with radium-223 or placebo.¹¹⁶ Radium-223 was well tolerated except for the appearance of grade 2 diarrhoea and thrombocytopenia.¹¹⁶ Treatment with radium-223 was associated with improvement in overall survival (14.0 months versus 11.2 months; HR 0.7, $P=0.002$) and secondary end points such as time to first symptomatic skeletal-related event, time to PSA progression and time to increase in alkaline phosphatase.¹¹⁶ Radium-223 was approved by the FDA in May 2013 and became the fifth agent to be FDA-approved since April 2010 for the treatment of CRPC, which has shown improvement in survival.

Conclusions

The current literature regarding prostate cancer therapy in the elderly supports the SIOG consensus that older men with prostate cancer should be managed according to their individual health status, which is driven by the severity of associated comorbid conditions, and not solely according to biological age.³⁰ In elderly patients with prostate cancers assessment before making treatment decisions should include evaluation of comorbidities, functional status, nutritional status, and geriatric outcomes. It is important that optimal care is not denied to these patients solely based on their age as when fit, elderly patients seem to tolerate and benefit from the therapies generally used for prostate cancer. Furthermore, a range of recently approved agents with different mechanisms of action, including the ARB enzalutamide, the androgen synthesis inhibitor abiraterone acetate, the micro-tubule inhibitor cabazitaxel, the sipuleucel-T vaccine, and the radionuclide radium-223 are well tolerated in elderly men and have demonstrated improved survival, bolstering our armamentarium for the management these patients (Figure 1). Despite availability of newer agents, it is important that the elderly are not subjected to unnecessary treatments if comorbidities are present, especially men with indolent disease. As we confront an ageing population, we will have to modify and modulate our approach to manage these patients on the basis of their individual clinical situation. Existing data are often restricted to men aged <75 years, leaving us to make assumptions for the decision on the treatment of older patients. Further studies directed at a population aged ≥ 75 years are necessary to help direct our approach to disease management.

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Key points

- Elderly (aged ≥ 70 years) patients with prostate cancer constitute a unique patient population
- On the one hand, elderly patients are often denied effective treatments because of fear of toxicity or diminished efficacy merely based on their age
- On the other hand, elderly patients can be unduly subjected to intense therapies despite multiple comorbidities in the setting of indolent disease
- It is important to individualize therapy based on the comorbidities, functional status, nutritional status and aggressiveness of disease rather than age alone

Figure 1.

Treatment options for patients with metastatic CRPC. *Sipuleucel-T and radium-223 are not approved in patients with visceral metastasis.

Table 1
Results of therapy in elderly prostate cancer patients—data from major studies

Study	Study specification	Patient characteristics	Findings
<i>Radical prostatectomy</i>			
Siddiqui <i>et al.</i> (2006) ²¹	Single-institution chart review between 1987–1995	Patients with prostate cancer treated with retropubic radical prostatectomy were classified into the age-categories of 55, 55–59, 60–64, 65–69 and 70 years	The risk of cancer death was lower in patients aged 70 years (HR 0.53, 95% CI 0.30–0.90), compared to younger patients
Begg <i>et al.</i> (2002) ¹⁷	Evaluation of patients from SEER database between 1992–1996	Patients who underwent radical prostatectomy were evaluated for health-related outcomes after surgery	Rates of complications were similar between men aged 65–69 and 70–74 years
<i>Radiotherapy</i>			
Abdollah <i>et al.</i> (2012) ³³	A population-based cohort study between 1992–2005	Men with cT1–T2 prostate cancer were treated with radiotherapy or observation	Radiotherapy was associated with improved 10-year cancer-specific mortality rates in elderly (5.7% vs 6.5%, HR 0.81, 95% CI 0.67–0.98)
Fiorica <i>et al.</i> (2010) ³⁶	Chart review of patients between 2000–2007	Patients aged 75 years with prostate cancer received radiotherapy in combination with a 6-month androgen suppression therapy	The compliance with radiotherapy was good and the rate of toxicity was acceptable in elderly patients. The 5-year overall survival rate was 78% and actuarial disease-free survival was 75.8%
Geinitz <i>et al.</i> (2005) ³⁹	Cohort study of patients between January 1994 and May 2000	Patients aged 75 years or 75 years received 70 Gy dose of 3D conformal radiation therapy	There were no significant differences in acute or late adverse effects between the two groups. The frequency of grade 3 late symptoms was low and in the range of 0–4% in both groups. Patients aged 75 years had a better biochemical recurrence-free survival at 4 years
Jani <i>et al.</i> (2005) ⁴⁰	Single-institution retrospective cohort study	Patients with non-metastatic prostate cancer receiving radiotherapy were divided into four major age-categories: <60 years, 60–69 years, 70–74 years, and 75 years to study the acute and chronic radiation therapy toxicity	The toxicity rates were not significantly different as a function of age for either acute or late genitourinary toxicity ($P = 0.10$ and $P = 0.22$, respectively) or acute or late gastrointestinal toxicity ($P = 0.19$ and $P = 0.09$, respectively)
<i>Androgen deprivation therapy</i>			
Cora <i>et al.</i> (2013) ⁸⁴	Phase III trial multinational, randomized, double-blind study	Patients with CRPC post disease progression on docetaxel-based chemotherapy were treated with enzalutamide	A similar improvement in overall survival, progression-free survival and reduction in PSA levels was observed in patients >75 years compared to patients <75 years
Efstathiou <i>et al.</i> (2008) ⁶⁹	Analysis of phase III trial	Patients with T2c–T4 prostate cancer received radiotherapy and 4 months of goserelin and then were randomized to no additional therapy or 24 months adjuvant goserelin	The cardiovascular mortality was similar with placebo and goserelin in patients aged >70 years
<i>Chemotherapy</i>			
Berthold <i>et al.</i> (2008) ¹⁰¹	Updated survival analysis of TAX 327	Men with CRPC were randomized to receive docetaxel administered weekly or every 3 weeks, or mitoxantrone every 3 weeks, each in combination with prednisone	The HR for survival in patients younger and older than 68 years was similar (0.81 and 0.77, respectively) for docetaxel given every 3 weeks
Italiano <i>et al.</i> (2009) ¹⁰²	Chart review of patients in nine French tertiary care cancer centres from 2000 to 2007	Patients aged 75 years with CRPC were treated with first-line docetaxel every 3 weeks	Safety and efficacy profile of docetaxel in the elderly cohort was similar to the younger patients in TAX327 study. Median PFS was 7.4 months and median overall survival was 15 months. The incidence of grade 3 or 4 adverse events was 46%
Beer <i>et al.</i> (2003) ⁹⁵	Pooled data from two phase II clinical trials	Men with metastatic CRPC aged >70 years were compared with patients aged	The PSA response rate ($P = 0.75$), measurable disease response rate ($P = 0.43$), time to progression ($P = 0.28$), and survival

Study	Study specification	Patient characteristics	Findings
		<70 years, for response and toxicity with weekly docetaxel	($P=0.52$) were not affected by age in both univariate and multivariate analyses. Similarly, haematological and nonhematological toxicity >grade 2 were similar in younger and elderly patients
Heidenreich <i>et al.</i> ¹⁰⁴ (2014)	Prospective cohort study	Patients aged ≥65 years with mCRPC unresponsive to docetaxel received cabazitaxel	Treatment related adverse effects were similar in the two groups and were manageable in the elderly population with metastatic CRPC

Abbreviations: CRPC, castration resistant prostate cancer; PFS, progression free survival; PSA, prostate specific antigen.