Annals of Oncology Advance Access published June 27, 2013

clinical practice guidelines

Annals of Oncology 00: 1–9, 2013
doi:10.1093/annonc/mdt208

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

A. Horwich[1], C. Parker[1], T. de Reijke[2] & V. Kataja[3], on behalf of the ESMO Guidelines Working Group*

[1]*Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK;* [2]*Department of Urology, Academic Medical Center, Amsterdam, The Netherlands;* [3]*Cancer Centre, Kuopio University Hospital, Kuopio, Finland*

incidence and mortality

The age-standardised incidence of prostate cancer in the European Union (EU) was 65/100 000 men in 2008, ranging in different member states from 18 per 100 000 in Greece to 126 per 100 000 in Ireland depending predominantly on the prevalence of prostate-specific antigen (PSA) screening [1]. Age-standardised mortality rates are predominantly between 15 and 37 per 100 000 [2]. It is the most common cancer in men with an estimated 382 000 cases occurring during 2008 in Europe. The mortality in the EU is 30.6/100 000 men/year and almost 90 000 deaths from prostate cancer occurred in Europe in 2008, making it the third most common cancer death in men [2].

Subclinical prostate cancer is common in men >50 years. Population-based screening of healthy men between 55 and 69 years old using PSA testing reduces prostate cancer mortality by an estimated 20%. Six trials and a meta-analysis have been published evaluating the role of screening, of which three were originally designed to evaluate prostate cancer mortality [3, 4]. After a median follow-up of 11 years the European screening trial demonstrated a relative reduction in the risk of prostate cancer mortality of 21% for the screened population (29% if adjusted for non-compliance). However, 1055 men needed to be invited for screening and 37 patients needed to be treated to prevent one patient from dying from prostate cancer. At 11 years follow-up, there was no reduction in overall mortality between the screened and non-screened population. In a further evaluation of the European screening study, it was shown that the benefit of screening was diminished by loss of quality-adjusted life years [5].

Recommendation: population-based screening for prostate cancer reduces prostate cancer mortality at the expense of a high over-treatment rate [I, B].

Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: February 2002, last update May 2013. This publication supersedes the previously published version-Ann Oncol 2010; 21 (Suppl. 5): v129–v133.

diagnosis

Based on the digital rectal examination (DRE), 23%–45% of prostate cancers are missed and if prostate cancer is diagnosed on the basis of DRE ~50% are locally advanced tumours. A DRE is not a very sensitive and reproducible investigation and has a low positive predictive value (PPV), but DRE in combination with serum PSA should be done in an appropriately counselled patient in whom there is clinical suspicion of prostate cancer or in those who wish further investigation for the presence of prostate cancer. A number of factors improve the predictive power of PSA level in identifying cancer [6]. A new biomarker for prostate cancer has recently been introduced, the urinary PCA3 test. Some studies have shown that this test was superior to total PSA [7], and the PCA3 test is now registered for the indication to perform a re-biopsy.

Recommendation: the decision whether or not to have a prostate biopsy should be made in the light of DRE findings, prostate size, ethnicity, age, comorbidities, family history, patient values and history of previous biopsy, as well as on the PSA level. In case of an elevated PSA and negative initial biopsies, a PCA3 test can be carried out to determine whether re-biopsies are indicated [II, B].

Sampling error is inherent in the process of prostate biopsies. Most of the aggressive tumours are located in the peripheral zone and therefore, at least six biopsies (three from each lobe) should be taken from this zone. However, 20%–35% of the tumours will be missed if only these areas are sampled; therefore, the anterolateral area of the prostate should be sampled as well. A recent meta-analysis demonstrated an improvement in the prostate cancer detection rate of 25% if 12 biopsies were taken instead of six, especially if the prostate volume exceeded 40 cc [8]. Initial saturation biopsies were not of any advantage.

Recommendation: a prostate biopsy should be carried out under antibiotic cover with transrectal ultrasound (TRUS) guidance, and a minimum of eight cores obtained [II, A].

The most dominant Gleason pattern and the pattern with the highest Gleason grade determine the Gleason score [9] because

tumours with a tertiary Gleason grade 4 or 5 behave more like a Gleason score 3+4 or 3+5 than the sum of the two most dominant patterns. Reporting of Gleason grades 1 and 2 should be avoided on biopsies. The extent of tumour in biopsies correlates with the pathological stage, tumour volume in the prostate and chance of positive margins.

Recommendation: the maximum length of cancer involvement of each core and the commonest and the worst Gleason grades should be reported in the biopsies, as they help predict pathological stage and progression-free survival [III, A].

staging and risk assessment

General health and co-morbidities should be assessed. Patients who are not considered suitable for treatment with curative intent due to poor general health do not normally require staging investigations. Clinical T stage (Table 1) should be evaluated by DRE supplemented, when clinically relevant, with magnetic resonance imaging (MRI). Experience in the interpretation of the MRI is essential, and contrast-enhanced MRI and 3 Tesla MRI can improve sensitivity of local staging of the prostate cancer. Preoperative MRI can help to identify those patients in whom a nerve-sparing radical prostatectomy can be carried out. Clinically localised prostate cancer should be categorised as low-, intermediate- or high-risk and a widely used classification (Table 2) identifies those with respectively a 90%, 60% and 30% probability of biochemical control at 5 years [10]. Other prognostic nomograms may help to inform patient choice [11].

Recommendation: localised disease should be classified as low-, intermediate- or high-risk as a guide to staging and therapy [III, A].

Table 1. Prostate cancer staging summary (Seventh Edition of the AJCC/UICC Cancer Staging Manual)

T1	Not palpable or visible
T1a	≤5%
T1b	>5%
T1c	Needle biopsy
T2	Confined within prostate
T2a	≤half of 1 lobe
T2b	>half of 1 lobe
T2c	Both lobes
T3a	Through prostatic capsule
T3b	Invading seminal vesicle
T4	Fixed or invading adjacent structure
N1	Regional nodes
M1a	Non-regional nodes
M1b	Bone
M1c	Other sites

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Table 2. Localised prostate cancer: risk groups (NCCN) [3]

1. Low-risk: all of T1 or T2a, Gleason <7 PSA <10
2. Intermediate-risk: between low and high
3. High-risk: any of T3 or T4, Gleason >7 PSA >20

Low-risk: within the low-risk category, higher percent positive cores, maximum length of cancer involvement, PSA density and lower free/total PSA ratio are associated with the risk of understaging compared with findings after prostatectomy [12].

Recommendation: bone imaging is not routinely recommended for men with low-risk disease [II, B].

Intermediate-risk: a study of criteria for staging with isotope bone scan [13] found that unless the primary Gleason grade was at least 4, of men with Gleason <8, PSA <20 and stage <T4 the bone scans were positive in only 1% (95% CI 0.3% to 4%). The general guidelines suggest that bone scintigraphy should be considered if bone metastases are suspected clinically, if the Gleason score is 4+3 or serum PSA is >10 ng/ml [13].

Recommendation: the sensitivity of pelvic imaging is lower than surgical lymph node staging, but those patients with intermediate-risk disease to be treated with radical radiotherapy (RT) should ideally have pelvic MRI. Intermediate-risk patients having a radical prostatectomy should have discussion about risk/benefit of lymph node dissection based on nomogram estimates [III, B].

Recommendation: For high-risk disease, bone scintigraphy should be carried out and an MRI of the pelvis should be considered [IV, B].

management of local/locoregional disease

There is no consensus regarding optimum management of localised disease. Options include watchful waiting, active surveillance, open, laparoscopic or robotic-assisted radical prostatectomy, external beam RT, and brachytherapy. Cryotherapy, high-intensity focused ultrasound (HIFU) and focal therapy are not recommended as standard initial treatment, but rather are regarded as options in development. Patients should be informed of the potential benefits and harms of the different options. Given the range of treatment options and their side-effects, men should have the opportunity to consult with both the urologist and the radiation oncologist. Men should be warned that treatment for prostate cancer may cause sexual dysfunction, infertility, rectal/voiding problems and incontinence.

low and intermediate-risk groups

One randomised, controlled trial, PIVOT, has compared radical prostatectomy and watchful waiting in men with PSA-detected cancers [14]. In the low-risk subgroup of 296 men, the risk of death from prostate cancer was <3% at 12 years, with no significant benefit of surgery. Indeed, the trend both in terms of prostate cancer-specific mortality [hazard ratio (HR) 1.48; 95% confidence interval (CI): 0.42–5.24)] and overall mortality (HR

1.15; 95% CI: 0.80–1.66), favoured watchful waiting rather than surgery.

The Scandinavian Prostate Cancer Group Study 4 was the first randomised, controlled trial comparing radical prostatectomy versus watchful waiting [15]. Eligible patients were <75 years and had newly diagnosed clinically localised prostate cancer with a negative bone scan, a PSA of <50 ng/ml and a life expectancy of ≥10 years. They were recruited in Scandinavia during the early 1990s, at a time when PSA testing was not routinely carried out, and the results may not be applicable to screen-detected cancers. Many of the 695 patients had high-risk disease, with 18% having a PSA >20 ng/ml and 13% a Gleason score of 8–10. With 11 years median follow-up, 137 men in the surgery group and 156 in the watchful waiting group had died ($P = 0.09$). The actuarial risk of death from prostate cancer at 12 years was 12.5% for surgery compared with 17.9% for watchful waiting ($P = 0.03$). Put another way, the number needed to treat (NNT) to avoid one death from prostate cancer was 18.5. This beneficial impact of surgery on prostate cancer mortality was restricted to men aged ≤65 years. Radical prostatectomy increased the rate of erectile dysfunction by 35% (80% versus 45%), and urinary leakage by 28% (49% versus 21%), in comparison with watchful waiting [16] but these toxicity rates may not be generalisable to high-volume surgical centres and did not appear to lead to a worse overall quality of life compared with the watchful waiting group [17].

Recommendation: in men with low-risk disease, no benefit for active treatment has been demonstrated in overall survival (OS). Observation should be discussed and should be an option for these patients. Options for patients with intermediate-risk prostate cancer include radical prostatectomy, external beam RT plus androgen deprivation therapy (ADT) or high-dose rate brachytherapy. Watchful waiting with delayed hormone therapy is an option for men who are not suitable for radical treatment [I, A].

high-risk or locally advanced group

The standard radical approach is based on RT, though prostatectomy with extended lymphadenectomy can be an option in highly selected cases. For high-risk cancers there is abundant level I evidence that the combination of RT and ADT leads to significantly higher OS rates when compared with RT alone [18] and to ADT alone [19, 20]. Hormone therapy alone is not recommended and the case for adding radical local treatment for men with locally advanced disease is based on two randomised, controlled trials. The SPCG-7 trial, in which 875 men (T2–3; PSA <70 ng/ml; N0; M0) received 3 months of combined androgen blockade (CAB) followed by flutamide monotherapy, and were randomised whether or not to receive radical RT to the prostate [19], showed a beneficial impact of radical RT in terms of cause-specific (11.9% versus 23.9%, $P < 0.001$), and overall mortality (29.6% versus 39.4%, $P = 0.004$). The NCIC/MRC trial randomised high-risk patients to either lifelong ADT alone or to ADT plus RT. The addition of RT improved the 7-year survival probability from 66% to 74% ($P = 0.003$) [20]. Watchful waiting with delayed hormone therapy is an option for asymptomatic men who are not suitable for or are unwilling to have radical treatment.

Recommendation: high-risk or locally advanced prostate cancer patients should be offered external beam RT plus hormone treatment for at least 2 years. Radical prostatectomy plus extended lymphadenectomy can be considered in highly selected cases [I, B].

neo-adjuvant and adjuvant treatment

In TROG 96–01 [21] 818 men with locally advanced prostate cancer were randomly assigned to RT alone, RT plus 3 months neo-adjuvant and concurrent CAB or RT plus 6 months CAB. Compared with RT alone, the use of 6 months of hormone therapy significantly improved PSA progression (HR 0.57 [0.46–0.72]), prostate-cancer-specific survival (HR 0.49 [0.32–0.74], $P = 0.04$) and all-cause mortality (HR 0.63 [0.48–0.83]). This result is supported by an American study [22]. In the RTOG trial 86–10, 456 patients with T2–4 disease received CAB for 2 months before and during RT, or RT alone [23]. There was a statistically significant improvement in 10-year prostate cancer-specific mortality (23% versus 36%; $P = 0.01$) with the addition of hormone therapy.

In RTOG 9202 [24] 1554 patients received 4 months of neo-adjuvant and concurrent CAB plus radical RT and were randomised to receive an additional 2 years of adjuvant androgen deprivation or not. In an unplanned subgroup analysis, the addition of adjuvant therapy improved OS in those with Gleason score 8–10 (81.0% versus 70.7%, $P = 0.044$). The EORTC 22961 [25] trial randomised 970 men between 6 months and 36 months of androgen deprivation in addition to radical RT. The 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively.

Men starting luteinizing hormone-releasing hormone (LHRH) agonist therapy should be informed that regular exercise may be helpful to reduce fatigue and improve quality of life [26].

Recommendation: neoadjuvant LHRH agonist therapy for 4–6 months is recommended for men receiving radical RT for high-risk disease, and this should be considered also for men with intermediate-risk disease. Adjuvant hormonal therapy for 2 to 3 years is recommended for men receiving neo-adjuvant hormonal therapy and radical RT who are at high risk of prostate cancer mortality [I, A].

Bicalutamide 150 mg daily was evaluated for locally advanced disease in a subgroup analysis of one trial but was compared with placebo rather than an LHRH agonist. It can be considered as an alternative adjuvant to LHRH agonist therapy in men who place a high value on retaining sexual function during treatment [27]. Men starting long-term (>6 months) bicalutamide should consider prophylactic RT to both breast buds within the first month of treatment or use of tamoxifen [28].

Recommendation: adjuvant hormone therapy can be based on bicalutamide 150 mg daily rather than an LHRH agonist in men who prefer its toxicity profile and understand that the data on outcomes are limited [II, C].

Three randomised trials, EORTC 22911, SWOG 8794 and ARO 96–02, have compared post-op RT versus observation after radical prostatectomy in patients with locally advanced disease, but they did not have sensitive PSA monitoring and early RT salvage in the control arms, and current trials are addressing this. Each trial has shown an advantage to postoperative RT in

terms of PSA failure, but the impact on OS is less clear. SWOG 8794 included 425 men and reported that OS was improved with adjuvant radiation (HR 0.72; 95% CI: 0.55, 0.96; $P = 0.023$). However, EORTC 22911, which included 1005 men [29] found no OS benefit (10-year OS 76.9% for adjuvant radiation versus 80.7% for observation).

Radiotherapy to the prostate bed has a risk of adverse effects on urinary, bowel and sexual function. For example, the SWOG 8794 trial [30] reported urethral strictures in 17.8% of men randomised to adjuvant RT versus 9.5% in those randomised to observation [relative risk (RR) 1.9; 95% CI: 1.1–3.1; $P = 0.02$]. Total urinary incontinence was seen in 6.5% versus 2.8% (RR 2.3; 95% CI: 0.9–5.9; $P = 0.11$), and rectal complications in 3.3% versus 0% ($P = 0.02$).

Recommendation: immediate postoperative RT after radical prostatectomy can be considered but is not routinely recommended. Adjuvant hormone therapy after radical prostatectomy is not recommended. Patients with positive surgical margins or extracapsular extension after radical prostatectomy should be informed about the pros and cons of adjuvant RT [I, C].

treatment of relapse after radical therapy

In patients with a biochemical relapse following radical prostatectomy, biopsy of the prostatic bed should not be carried out. There are no randomised trials comparing salvage RT versus observation in men with PSA failure after radical prostatectomy. A retrospective analysis of men with PSA failure after surgery compared the long-term outcome of those managed by observation ($n = 397$) with that of those managed by salvage RT ($n = 160$) [31]. A pooled analysis of trials of intermittent androgen deprivation (IAD) published up till September 2012 was based on a total of 5508 patients and did not reveal any significant differences in time-to-event outcomes [HR for PFS 0.96 (95% CI: 0.76–1.20), HR for OS 1.02 (95% CI: 0.94–1.11)] [32]. There were 116 deaths from prostate cancer for analysis. Salvage RT was associated with a significant reduction in prostate cancer mortality (HR 0.32; 95% CI: 0.19–0.54; $P < 0.001$). The reduction in prostate cancer mortality associated with salvage RT was greatest in men with a PSA doubling time of <6 months.

Recommendation: following radical prostatectomy patients should have their serum PSA levels monitored with salvage RT to the prostate bed recommended in the event of PSA failure, assuming that there are no metastases. Salvage RT should start early [III, B].

ADT for relapse following radical prostatectomy or RT has been evaluated in retrospective series. For example, Moul et al. [33] observed no survival benefit, although time to clinical metastases was delayed by early androgen treatment. IAD was studied in a randomised trial which included 1386 patients with a PSA at relapse of >3.0 ng/ml more than 1 year after radical or salvage RT with or without neo/adjuvant hormonal therapy (≤1-year duration) for localised prostate cancer. Several quality of life domains were improved. Median OS was 8.8 and 9.1 years for the IAD and continuous androgen deprivation arm, respectively [34].

Recommendation: hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have symptomatic local disease progression or proven metastases, or PSA doubling time <3 months. IAD is not inferior to continuous androgen deprivation and has quality-of-life benefits [I, C].

metastatic disease

Androgen suppression using bilateral orchiectomy or an LHRH agonist/antagonist should be first-line treatment. Short-course anti-androgen should be used to prevent disease flare on starting an LHRH agonist. The recently developed LHRH antagonists appear to offer equivalent testosterone reduction without the need for an anti-androgen to control transient testosterone surge. Mature results are awaited of IAD approaches, though early results suggested equivalent efficacy to continuous hormone ablation [35]. A large international phase III trial [36] registered over 3000 patients with metastatic hormone-naïve prostate cancer, and randomised the 1535 who achieved PSA <4 ng/ml on combined androgen blockade to either IAD or continuous AD. With a median follow-up of 9.8 years, median survival was 5.8 years on continuous AD versus 5.1 in the IAD group (HR 1.1 90% CI: 0.99–1.23) with the conclusion that non-inferiority of IAD was not established.

A number of trials have examined combined androgen blockade based on the addition of anti-androgens to LHRH agonist therapy (or orchiectomy). In a meta-analysis of 27 trials, the 5-year survival was 25.4% with combined androgen blockade compared with 23.6% for androgen deprivation alone ($P = 0.11$) [37]. However, an analysis of trials combining a non-steroidal anti-androgen with androgen deprivation suggested a small survival advantage (27.6% versus 24.7%, $P = 0.005$). A larger difference was found with earlier trials when LHRH delivery may have been less reliable and a more recent large trial comparing orchiectomy with orchiectomy plus flutamide [38] did not demonstrate any benefit of the combined androgen blockade but did show inferior quality of life.

Recommendation: considering the possible minimal survival benefit together with the cost and toxicity of the additional anti-androgen, first-line hormonal management of metastatic prostate cancer should be based on chemical or surgical castration only [I, B].

Second-line hormone therapies include anti-androgens, corticosteroids, oestrogens and CYP17 inhibitors, and can be effective in those relapsing on androgen deprivation. For example, the anti-androgen flutamide achieves objective responses in about 15% of patients with PSA progression but with no survival benefit. Low dose corticosteroids decrease adrenal function including production of androgens and lead to responses in approximately one-third of cases. Oestrogens can also lead to responses in 20%–40% of patients who have failed ADT though side-effects including gastrointestinal irritation, fluid retention and venous thrombosis are not uncommon. In those that have responded to the addition of anti-androgen, there can be a further response to withdrawal of the anti-androgen. A number of recently developed hormone therapies have been evaluated in the post-docetaxel setting and have been shown to be effective in prolonging survival. These include abiraterone acetate [39] and enzalutamide [40]. Also, the trial of abiraterone pre-docetaxel in castration-resistant prostate cancer

(CRPC) has been reported [41]. More than 1000 patients were randomised between abiraterone plus prednisone versus prednisone alone, and the abiraterone arm demonstrated improved radiographic progression-free survival (16.5 versus 8.3 months), and a strong trend to improved OS (median not reached versus 27.2 months).

Recommendation: patients who develop CRPC should continue androgen suppression and be considered for further hormone therapies; chemotherapy might be preferable in those with poor initial hormone response or severe symptoms. In patients progressing following docetaxel, treatment with abiraterone, or enzalutamide, should be discussed if not used previously [II, A].

In a large international multicentre stage III trial (TAX327) [42, 43], two different schedules of docetaxel with prednisone were compared with a combination of mitoxantrone and prednisone. One thousand and six patients were recruited and randomly assigned between weekly docetaxel at 30 mg/m^2 for five out of every 6 weeks, 75 mg/m^2 with docetaxel every 3 weeks and mitoxantrone 12 mg/m^2 every 3 weeks. Patients in all arms of the trial received prednisone. The median survival was 19.2 months in the 3-weekly docetaxel arm, 17.8 months in the weekly docetaxel arm and 16.3 months after mitoxantrone. Slightly less than one-quarter treated with docetaxel had a significant improvement in the quality of life. Almost half of the patients treated with docetaxel had a 50% decrease in PSA. The side-effects of docetaxel chemotherapy included grade III to IV neutropenia in 32% of patients treated with 3-weekly docetaxel but in only 1.5% of those treated with weekly docetaxel. Other side-effects included fatigue, alopecia, diarrhoea, neuropathy, peripheral oedema and male dystrophy. The conclusion was that 3-weekly docetaxel was superior to the other treatments in its palliative effects and in prolongation of survival. Docetaxel with estramustine [44] is also an effective regimen but appears to be more toxic. The standard 3-weekly schedule was compared to administering 50 mg/m^2 every 2 weeks, in a multicentre trial in 346 patients with metastatic CRPC from Finland, Ireland and Sweden [45]. The 2-weekly schedule seemed as effective but may be better tolerated, and merits further evaluation. There may be an initial PSA rise in some patients responding to chemotherapy. The best level of PSA response to use as a surrogate end point for survival gain is controversial and, unless there is unequivocal clinical progression response, assessment should be delayed until about 12 weeks. Mitoxantrone can be considered if there is a contraindication to docetaxel, but is inferior in palliation and does not prolong survival.

Recommendation: docetaxel using a 3-weekly schedule should be considered for symptomatic, castration-resistant disease [I, A].

The novel tubulin-binding agent cabazitaxel was studied in combination with prednisone in a prospective randomised trial against mitoxantrone plus prednisone in 755 patients progressing on or after docetaxel. It demonstrated an improved progression-free survival (2.9 versus 1.4 months) and improved median survival (15.1 versus 12.7 months).The HR for death was 0.7 ($P < 0.0001$) [46]. Toxicity of this treatment should be considered.

Recommendation: cabazitaxel is more effective than mitoxantrone in patients previously treated with docetaxel [I, B].

A prospective, randomised trial in 288 patients with painful bone metastases showed no benefit in either speed of onset or duration of pain relief from 30 Gy in 10 fractions compared with 8 Gy in a single fraction [47]. This has been confirmed in a number of trials and in a systematic review [48].

Recommendation: external beam RT should be offered for patients with a moderate number of painful bone metastases (1×8 Gy has equal pain-reducing efficacy to multifraction schedules) [I, A].

A single treatment with, e.g. strontium-89, is more effective than placebo in reducing pain due to bone metastases [49]. A Canadian trial [50] analysed 126 men who had received external beam RT to palliate bone metastases, and showed that strontium prolonged time to further bone pain. Samarium-153 has also been studied in randomised trials, which included patients with prostate cancer [51]. The ALSYMPCA trial studied radium-223 versus placebo in 921 men with bone-metastatic CRPC. It showed an OS benefit for radium-223 (median 14.9 months versus 11.3 months; HR 0.695; 95% CI: 0.581–0.832; $P = 0.00007$), a delay in time to first skeletal-related event (SRE) (median 15.6 months versus 9.8 months; HR, 0.658; 95% CI, 0.522–0.830; $P < 0.001$) and a favourable toxicity profile [52], and subject to regulatory approval this may become a new treatment option for symptomatic patients.

Recommendation: bone targeted therapy with one of the beta particle emitting radionuclides should be considered for patients with painful bone metastases [II, B].

Saad et al. [53] reported a prospective, randomised three-arm trial in patients with CRPC, which compared zoledronic acid at 4 mg i.v. every 3 weeks, 8 mg i.v. every 3 weeks or placebo. Patients continued with ADT or other anticancer therapies as indicated. There were more than 200 men in each arm of the study. The primary end point was time to first SRE such as pathological fracture, spinal cord compression, surgery or RT for bone pain or a change in anticancer treatment for bone pain. The higher dose of zoledronic acid caused renal damage and during the study those randomly assigned to the 8 mg dosage had dose reduction to 4 mg. At 15 months, there were fewer SREs in men originally randomised to the 4 mg dosage than in those randomised to placebo (33% versus 44%, $P = 0.02$). However, the difference between those randomly assigned to zoledronic acid at 8 mg and placebo was not significant, and there were no differences in disease progression, OS or quality of life scores among the groups. Thus, the use of zoledronic acid in this patient population must be judged by balancing this level of benefit with the risk of toxicity. Toxic effects of bisphosphonates include anaemia, fever, oedema, hypocalcaemia, fatigue and myalgia and osteonecrosis of the mandible and dental health evaluation should precede treatment.

A single large phase III trial in men with bone metastases from CRPC has compared denosumab versus zoledronic acid [54]. Denosumab was superior with respect to time to SREs [HR 0.82 (0.71–0.95), $P = 0.0002$], but was associated with an increased risk of hypocalcaemia (13% versus 6%). Osteonecrosis of the mandible was seen in both the arms of the trial. There was no difference in OS.

Recommendation: in patients with bone metastases from CRPC at high risk for clinically relevant SREs, denosumab or zoledronic acid can be recommended, and a large trial found

Table 3. Summary of recommendations

Topic	Recommendations
Incidence and mortality Diagnosis	• Population-based screening for prostate cancer reduces prostate cancer mortality at the expense of a high over-treatment rate [I, B]. • The decision whether or not to have a prostate biopsy should be made in the light of DRE findings, prostate size, ethnicity, age, comorbidities, family history, patient values and history of previous biopsy, as well as on the PSA level. In case of an elevated PSA and negative initial biopsies, a PCA3 test can be carried out to determine whether re-biopsies are indicated [II, B]. • A prostate biopsy should be carried out under antibiotic cover with transrectal ultrasound (TRUS) guidance, and a minimum of eight cores obtained [II, A]. • The maximum length of cancer involvement of each core and the commonest and the worst Gleason grades should be reported in the biopsies, as they help predict pathological stage and progression-free survival [III, A].
Staging and risk assessment	• Localised disease should be classified as low-, intermediate- or high-risk as a guide to staging and therapy [III, A]. • Bone imaging is not routinely recommended for men with low-risk disease [II, B]. • The sensitivity of pelvic imaging is lower than surgical lymph node staging, but those patients with intermediate-risk disease to be treated with radical radiotherapy (RT) should ideally have pelvic magnetic resonance imaging (MRI). Intermediate-risk patients having a radical prostatectomy should have discussion about risk–benefit of lymph node dissection based on nomogram estimates [III, B]. • Bone scintigraphy should be carried out and MRI of the pelvis should be considered [IV, B].
Management of local/loco-regional disease	• In men with low-risk disease, no benefit for active treatment has been demonstrated in overall survival (OS). Observation should be discussed and should be an option for these patients. Options for patients with intermediate-risk prostate cancer include radical prostatectomy, external beam RT plus androgen deprivation therapy (ADT) or high-dose rate brachytherapy. Watchful waiting with delayed hormone therapy is an option for men who are not suitable for radical treatment [I, A]. • High-risk or locally advanced prostate cancer patients should be offered external beam RT plus hormone treatment for at least 2 years. Radical prostatectomy plus extended lymphadenectomy can be considered in highly selected cases [I, B].
Neoadjuvant and adjuvant treatment	• Neoadjuvant LHRH agonist therapy for 4–6 months is recommended for men receiving radical RT for high-risk disease, and this should be considered also for men with intermediate-risk disease. Adjuvant hormonal therapy for 2 to 3 years is recommended for men receiving neo-adjuvant hormonal therapy and radical RT who are at high risk of prostate cancer mortality [I, A]. • Adjuvant hormone therapy can be based on bicalutamide 150 mg daily rather than an LHRH agonist in men who prefer its toxicity profile and understand that the data on outcomes are limited [II, C]. • Immediate postoperative RT after radical prostatectomy can be considered but is not routinely recommended. Adjuvant hormone therapy after radical prostatectomy is not recommended. Patients with positive surgical margins or extracapsular extension after radical prostatectomy should be informed about the pros and cons of adjuvant RT [I, C].
Treatment of relapse after radical therapy	• Following radical prostatectomy patients should have their serum PSA levels monitored with salvage RT to the prostate bed recommended in the event of PSA failure, assuming that there are no metastases. Salvage RT should start early [III, B]. • Hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have symptomatic local disease progression or proven metastases, or PSA doubling time <3 months. IAD is not inferior to continuous androgen deprivation and has quality-of-life benefits [I, C].
Metastatic disease	• Considering the possible minimal survival benefit together with the cost and toxicity of the additional anti-androgen, first-line hormonal management of metastatic prostate cancer should be based on chemical or surgical castration only [I, B]. • Patients who develop castration-resistant prostate cancer (CRPC) should continue androgen suppression and be considered for further hormone therapies; chemotherapy might be preferable in those with poor initial hormone response or severe symptoms. In patients progressing following docetaxel, treatment with abiraterone, or enzalutamide, should be discussed if not used previously [II, A]. • Docetaxel using a 3-weekly schedule should be considered for symptomatic, castration-resistant disease [I, A]. • Cabazitaxel is more effective than mitoxantrone in patients previously treated with docetaxel [I, B]. • External beam RT should be offered for patients with a moderate number of painful bone metastases (1×8 Gy has equal pain-reducing efficacy to multifraction schedules) [I, A]. • Bone targeted therapy with one of the beta particle emitting radionuclides should be considered for patients with painful bone metastases [II, B]. • In patients with bone metastases from CRPC at high risk for clinically relevant SREs, denosumab or zoledronic acid can be recommended, and a large trial found that denosumab delayed SREs for longer than zoledronic acid. Neither agent has been shown to prolong survival [I, B]. • MRI of the spine to detect subclinical cord compression should be considered in men with CRPC with vertebral metastases and back pain [III, B].

Continued

Table 3. *Continued*

Topic	Recommendations
Personalised medicine	• Patients with evidence of neuroendocrine change in their prostate cancer should be selected for chemotherapy rather than hormone therapy [IV, B].
Follow-up	• Routine DRE after local therapy is not required for asymptomatic patients while the PSA remains at baseline levels [II, B] [58]. • Biopsy of the prostate after RT should only be carried out in men with prostate cancer who are being considered for salvage local therapy (e.g. HIFU, cryotherapy, salvage surgery) [V, C]. • Chronic bowel symptoms after RT should be fully investigated by a gastroenterologist [V, B]. • Men on long-term androgen deprivation should be monitored for side-effects including osteoporosis [IV, B].

that denosumab delayed SREs for longer than zoledronic acid. Neither agent has been shown to prolong survival [I, B].

Spinal cord compression is a devastating complication of metastatic prostate cancer and early detection is critical for successful management. MRI is the preferred imaging technique [55]. A retrospective analysis of patients with metastatic prostate cancer and no symptoms or signs of spinal compression showed that MRI was able to identify cord compression in 16% and radiological evidence of spinal cord compromise in a further 11% [56].

Recommendation: MRI of the spine to detect subclinical cord compression should be considered in men with CRPC with vertebral metastases and back pain [III, B].

personalised medicine

Prostate cancer has a widely heterogeneous natural history. Though there are clear and important prognostic factors to guide on the need for treatment in various clinical contexts, there are no predictive biomarkers to indicate particular treatment modalities. Advanced disease progressing without a significant rise in PSA should be investigated for neuroendocrine change using biopsy or blood analyses for neuron-specific enolase and/or chromogranin A [57], since this indicates a low chance of response to endocrine therapies. In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

Recommendation: patients with evidence of neuroendocrine change in their prostate cancer should be selected for chemotherapy rather than hormone therapy [IV, B].

follow-up

Recommendation: routine DRE after local therapy is not required for asymptomatic patients while the PSA remains at baseline levels [II, B] [58].

Recommendation: biopsy of the prostate after RT should only be carried out in men with prostate cancer who are being considered for salvage local therapy (e.g. HIFU, cryotherapy, salvage surgery) [V, C].

Men developing bowel symptoms after RT should be evaluated for inflammatory bowel disease, a primary colorectal malignancy or a treatable radiation enteropathy [59].

Recommendation: chronic bowel symptoms after RT should be fully investigated by a gastroenterologist [V, B].

Androgen deprivation may cause hot flushes, lethargy, mood changes, osteoporosis, insulin resistance and muscle weakness.

Recommendation: men on long-term androgen deprivation should be monitored for side-effects including osteoporosis [IV, B] (See Table 3).

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

	Levels of evidence
I	Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
	Grades of recommendation
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,..), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

acknowledgements

This work was undertaken in The Royal Marsden NHS Foundation Trust which received a proportion of its funding from the NHS Executive; we acknowledge NHS funding to the NIHR Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NHS Executive. This work was supported by the Institute of Cancer Research (ICR), and Cancer Research UK [CUK] grant number C46/A3970 to the ICR Section of Radiotherapy.

conflict of interest

Prof. Horwich has reported that his institution is inventor of Abiraterone and receives royalty payments; no personal conflicts. Dr. Parker has reported honoraria from Amgen, Astellas, Bayer, Bristol-Myers Squibb, BN ImmunoTherapeutics, Janssen, Sanofi-Aventis, Takeda. Dr. de Reijke has reported consultancy/honoraria from Janssen, Ferring, Teva, Novartis, Amgen; advisory board of Dendreon. Prof. Kataja has reported institutional clinical research support from Sanofi-Aventis, Bayer Health Care, Orion Pharma and Merck; the arrangements do not involve personal financial support from the companies mentioned.

references

1. OECD/European Union. 'Cancer Incidence', in Health at a Glance: Europe 2010. OECD Publishing. 2010. http://dx.doi.org/10.1787/9789264090316–18-en.
2. Bray F, Lortet-Tieulent J, Ferlay J et al. Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer 2010; 46: 3040–3052.
3. Schroder FH, Hugosson J, Roobol MJ et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366: 981–990.
4. Andriole GL, Crawford ED, Grubb RL, III et al. Prostate cancer screening in the randomized prostate, lung, colorectal and ovarian cancer screening trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104: 125–132.
5. Heijnsdijk EA, Wever EM, Auvinen A et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012; 367: 595–605.
6. Thompson IM, Ankerst DP, Chi C et al. Assessing prostate cancer risk: results from the prostate cancer prevention trial. J Natl Cancer Inst 2006; 98: 529–534.
7. Hessels D, van Gils MP, van Hooij O et al. Predictive value of PCA3 in urinary sediments in determining clinic-pathologic characteristics of prostate cancer. Prostate 2010; 70: 10–16.
8. Scattoni V, Zlotta A, Montironi R et al. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. Eur Urol 2007; 52: 1309–1322.
9. Epstein JI, Allsbrook WC, Jr, Amin MB et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005; 29: 1228–1242.
10. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; 280: 969–974.
11. Shariat SF, Karakiewicz PI, Roehrborn CG et al. An updated catalog of prostate cancer predictive tools. Cancer 2008; 113: 3075–3099. Review.
12. Suardi N, Capitanio U, Chun FK et al. Currently used criteria for active surveillance in men with low-risk prostate cancer. An analysis of pathologic features. Cancer 2008; 113: 2068–2072.
13. O'Sullivan J, Norman AR, Cook GJ et al. Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. BJU Int 2003; 92: 685–689.
14. Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012; 367: 203–213.
15. Bill-Axelson A, Holmberg L, Filén F et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst 2008; 100: 1144–1154.
16. Steineck G, Helgesen F, Adolfsson J et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002; 347: 790–796.
17. Johansson E, Bill-Axelson A, Holmberg L et al. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the randomized Scandinavian prostate cancer group study number 4 (SPCG-4) clinical trial. Eur Urol 2009; 55: 422–430.
18. Bolla M, Van Tienhoven G, Warde P et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010; 11: 1066–1073.
19. Widmark A, Klepp O, Solberg A et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer: an open randomised phase III trial. Lancet 2009; 373: 301–308.
20. Warde P, Mason M, Ding K et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011; 378: 2104–2111.
21. Denham JW, Steigler A, Lamb DS et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised controlled trial. Lancet Oncol 2011; 12: 451–459.
22. D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004; 292: 821–827.
23. Roach M, 3rd, Bae K, Speight J et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. JCO 2008; 26: 585–591.
24. Hanks GE, Pajak TF, Porter A et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92–02. J Clin Oncol 2003; 21: 3972–3978.
25. Bolla M, de Reijke TM, Van Tienhoven G et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009; 360: 2516–2527.
26. Galvao DA, Taaffe DR, Spry N et al. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol 2010; 28: 340–347.
27. McLeod DG, Iversen P, See WA et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int 2006; 97: 247–254.
28. Kunath F, Keck B, Antes G et al. Tamoxifen for the management of breast events induced by non-steroidal antiandrogens in patients with prostate cancer: a systematic review. BMC Med 2012; 10: 96.
29. Bolla M, van Poppel H, Tombal B et al. Postoperative radiotherapy after radical prostatectomy for high risk prostate cancer: long term results of a randomized controlled trial (EORTC trial 22911). Lancet 2012; 380: 2018–2027.
30. Thompson IM, Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow up of a randomized clinical trial. J Urol 2009; 181: 956–962.
31. Trock BJ, Han M, Freedland SJ et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008; 299: 2760–2769.
32. Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. J Clin Oncol. 2013; 31: 2029–2036.

33. Moul JW, Wu H, Sun L et al. Early versus delayed hormonal therapy for prostate antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 2004; 171: 1141–1147.
34. Crook JM, O'Callaghan CJ, Duncan G et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012; 367: 895–903.
35. Calais da Silva FE, Bono AV, Whelan P et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol 2009; 55: 1269–1277.
36. Hussain M, Tangen CM, Berry DL et al. Intermittent versus continuous androgen deprivation in prostate cancer. NEJM 2013; 368: 1314–1325.
37. Prostate Cancer Trialists Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 2000; 355: 1491–1498.
38. Eisenberger MA, Blumenstein BA, Crawford ED et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998; 339: 1036–1042.
39. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995–2005.
40. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187–1197.
41. Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368: 138–148.
42. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502–1512.
43. Berthold DR, Pond GR, Soban F et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26: 242–245.
44. Petrylak DP, Tangen C, Hussain M et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351: 1513–1520.
45. Kellokumpu-Lehtinen P-L, Harmenberg U, Joensuu T et al. 2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. Lancet Oncol 2013: 14; 117–124.
46. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147–1154.
47. Price P, Hoskin PJ, Easton D et al. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiother Oncol 1986; 6: 247–255.
48. Chow E, Harris K, Fan G et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007; 25: 1423–1436.
49. Quilty PM, Kirk D, Bolger JJ et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. Radiother Oncol 1994; 31: 33–40.
50. Porter AT, McEwan AJ, Powe JE et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Radiat Oncol Biol Phys 1993; 25: 805–813.
51. Serafini AN, Houston SJ, Resche I et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J Clin Oncol 1998; 16: 1574–1581.
52. Parker C, Heinrich D, O'Sullivan JM et al. Overall survival benefit of radium-223 chloride (Alpharadin™) in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer (CRPC): a phase III randomized trial (ALSYMPCA). Eur J Cancer 2011; 47(Supp 2): 3.
53. Saad F, Gleason DM, Murray R et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004; 96: 879–882.
54. Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377: 813–822.
55. Loblaw DA, Perry J, Chambers A et al. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario practice guidelines initiative's neuro-oncology disease site group. J Clin Oncol 2003; 23: 2028–2037.
56. Venkitaraman R, Sohaib SA, Barbachano Y et al. Detection of occult spinal cord compression with magnetic resonance imaging of the spine. Clin Oncol 2007; 19: 528–531.
57. Beltran H, Tagawa ST, Park K et al. Challenges in recognizing treatment-related neuroendocrine prostate cancer. J Clin Oncol 2012; 30: e386–389.
58. Doneux A, Parker CC, Norman A et al. The utility of digital rectal examination after radical radiotherapy for prostate cancer. Clin Oncol 2005; 17: 172–173.
59. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. Lancet Oncol 2007; 8: 1007–1017.