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 [1, B].

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 50% probability of biochemical control at 5 years
[10]. Other prognostic nomograms may help to inform patient

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)

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Localisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Not palpable or visible</td>
</tr>
<tr>
<td>T1a</td>
<td>≤5%</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>T1c</td>
<td>Needle biopsy</td>
</tr>
<tr>
<td>T2</td>
<td>Confined within prostate</td>
</tr>
<tr>
<td>T2a</td>
<td>≤half of one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt;half of one lobe</td>
</tr>
<tr>
<td>T2c</td>
<td>Both lobes</td>
</tr>
<tr>
<td>T3a</td>
<td>Through prostatic capsule</td>
</tr>
<tr>
<td>T3b</td>
<td>Invading seminal vesicle</td>
</tr>
<tr>
<td>T4</td>
<td>Fixed or invading adjacent structure</td>
</tr>
<tr>
<td>N1</td>
<td>Regional nodes</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone</td>
</tr>
<tr>
<td>M1c</td>
<td>Other sites</td>
</tr>
</tbody>
</table>

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
cryo 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%
certainty interval (CI): 0.42–5.24)] and overall mortality (HR

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

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>all of T1 or T2a, Gleason ≤7 PSA ≤10</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>between low and high</td>
</tr>
<tr>
<td>High-risk</td>
<td>any of T3 or T4, Gleason ≥7 PSA ≥20</td>
</tr>
</tbody>
</table>

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed.

Used with the permission of the American Joint Committee on Cancer
(AJCC), Chicago, Illinois. The original source for this material is the AJCC
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 SPCCG-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 hormone 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 prostate 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 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 orchietomy 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-naive 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 orchietomy). 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 orchietomy with orchietomy 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...
mitoxantrone in patients previously treated with docetaxel [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/m² for five out of every 6 weeks, 75 mg/m² with docetaxel every 3 weeks and mitoxantrone 12 mg/m² 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/m² 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>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Incidence and mortality</td>
<td>Population-based screening for prostate cancer reduces prostate cancer mortality at the expense of a high over-treatment rate [I, B].</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>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].</td>
</tr>
<tr>
<td>Staging and risk assessment</td>
<td>Localised disease should be classified as low-, intermediate- or high-risk as a guide to staging and therapy [III, A].</td>
</tr>
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<td>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]. Bone imaging is not routinely recommended for men with low-risk disease [II, B]. 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].</td>
</tr>
<tr>
<td>Neoadjuvant and adjuvant treatment</td>
<td>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].</td>
</tr>
<tr>
<td>Treatment of relapse after radical therapy</td>
<td>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 &lt;3 months. IAD is not inferior to continuous androgen deprivation and has quality-of-life benefits [I, C].</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>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].</td>
</tr>
</tbody>
</table>
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].

**Recommendation**: 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).

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**Table 3. Continued**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalised medicine</td>
<td>• Patients with evidence of neuroendocrine change in their prostate cancer should be selected for chemotherapy rather than hormone therapy [IV, B].</td>
</tr>
</tbody>
</table>

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<tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td>• Chronic bowel symptoms after RT should be fully investigated by a gastroenterologist [V, B].</td>
</tr>
<tr>
<td></td>
<td>• Men on long-term androgen deprivation should be monitored for side-effects including osteoporosis [IV, B].</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>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</td>
</tr>
<tr>
<td>II</td>
<td>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</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case–control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grades of recommendation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...), optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>


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note

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

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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


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