Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker1, S. Gillessen2, A. Heidenreich3 & A. Horwich4, on behalf of the ESMO Guidelines Committee

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screening and early detection

Subclinical prostate cancer is common in men >50 years of age. Population-based screening of men aged between 55 and 69 years, using prostate-specific antigen (PSA) testing, has been evaluated in randomised trials [1, 2]. After a median follow-up of 13 years, the European screening trial demonstrated a relative reduction in the risk of prostate cancer mortality of 21% (29% if adjusted for non-compliance). However, 781 men needed to be invited for screening and 27 patients needed to be treated to prevent one death from prostate cancer. Risk-adapted early detection of prostate cancer using a baseline PSA level has also been evaluated in retrospective cohort studies. The baseline PSA at or before the age of 50 years is associated with the risk of prostate cancer mortality over the subsequent 25 years [3].

recommendations

• Population-based PSA screening for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and overtreatment and is not recommended [I, C].
• Testing for prostate cancer in asymptomatic men should not be done in men over the age of 70 years [I, B].

diagnosis and pathology

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination (DRE) [4]. High-grade prostate cancer can occur in men with a ‘normal’ PSA level. After a previous negative biopsy, indications for repeated biopsies include a rising PSA, suspicious DRE, abnormal multi-parametric magnetic resonance imaging (MRI), atypical small acinar proliferation or multifocal high-grade prostatic intraepithelial neoplasia.

recommendations

• A single elevated PSA level should not prompt a prostate biopsy, and should be verified by a second value [IV, B].
• The decision whether or not to have a prostate biopsy should be made in the light of DRE findings, ethnicity, age, co-morbidities, PSA values, free/total (f/t) PSA, history of previous biopsy and patient values [II, B].
• Transrectal ultrasound-guided prostate biopsy should be carried out under antibiotic cover and local anaesthesia, and a minimum of 10–12 cores obtained [II, B].
• Before repeat biopsy, multi-parametric MRI is recommended with a view to MRI-guided or MRI-transrectal ultrasound (TRUS) fusion biopsy [5] [III, B].

The most dominant Gleason pattern and the pattern with the highest Gleason grade determine the biopsy Gleason score [6]. Biopsy pathology should be reported using the International Society of Urologic Pathology recommendations.

recommendation

• The extent of involvement of each biopsy core, and the commonest and the worst Gleason grades should be reported [II, A].

staging and risk assessment

General health and co-morbidities should be assessed. Patients who are not suitable for treatment with curative intent, by virtue of poor general health, do not normally require staging investigations.

recommendation

• Localised disease should be classified as low-, intermediate- or high-risk (see Table 1) as a guide to prognosis and therapy [III, A].

Clinical T stage (Table 2) should be evaluated by DRE. MRI provides more accurate T staging and can inform surgical technique, both with respect to nerve sparing and wide excision of areas of potential extra-prostatic extension [9]. Within the low-risk category, higher % positive cores, length of core involvement, PSA
density and a lower f/t PSA ratio are associated with the risk of under-staging.

**recommendations**

- Patients with intermediate- or high-risk disease should have nodal staging using computed tomography (CT), MRI, choline positron emission tomography/CT (PET/CT) or pelvic nodal dissection [III, B].
- Patients with intermediate- or high-risk disease should be staged for metastases using technetium bone scan and thoraco-abdominal CT scan or whole-body MRI or choline PET/CT [III, B].

### management of local/locoregional disease

There is no consensus regarding optimum management of localised disease (Table 3). 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 be offered the opportunity to consult with both a urologist and a radiation oncologist. Men should be counselled that treatment of prostate cancer may cause sexual dysfunction, infertility, bowel and urinary problems.

Watchful waiting with delayed hormone therapy for symptomatic progression is an option for men who are not suitable for, or unwilling to have, treatment with curative intent. Curative treatment options include radical prostatectomy (RP), external beam radiotherapy and brachytherapy. Active surveillance is a strategy of close monitoring, typically using serum PSA, repeat prostate biopsies and/or MRI, keeping curative treatment in reserve for those with early evidence of disease progression [10].

Two randomised, controlled trials have compared RP and watchful waiting [11, 12]. The Scandinavian Prostate Cancer Group Study 4 accrued 695 men 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. With up to 23 years follow-up, 200 men in the surgery group and 247 in the watchful waiting group had died. The actuarial risk of death from prostate cancer at 18 years was 18% for surgery compared with 29% for watchful waiting (*P* = 0.001). RP increased the rate of erectile dysfunction (80% versus 45%), and urinary leakage (49% versus 21%) [13], but these side-effect rates may not be generalisable to high-volume surgical centres. The PIVOT trial recruited 731 North American men between 1994 and 2002 [12]. They were more representative of men with PSA-detected cancer, but these men had a higher than expected rate of co-morbidity. No significant difference was seen in overall survival [hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.71–1.08]. In the low-risk subgroup of 296 men, the risk of death from prostate cancer was <3% at 12 years, with no significant benefit for surgery. Indeed, the trend both in terms of prostate cancer-specific mortality (HR 1.48; 95% CI 0.42–5.24) and overall mortality (HR 1.15; 95% CI 0.80–1.66) favoured watchful waiting rather than surgery.

The case for adding radical local treatment for men with high-risk localised and locally advanced disease is based on two randomised, controlled trials. The Scandinavian Prostate Cancer Group Study 7 (SPCG-7) trial included 875 men who received 3 months of combined androgen blockade followed by flutamide monotherapy. They were randomised by whether or not they were to receive radical radiotherapy (RT) to the prostate [14]. It 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 androgen...
Table 3. Stage-matched therapeutic strategies

<table>
<thead>
<tr>
<th>Localised disease</th>
<th>Intermediate risk</th>
<th>High risk</th>
<th>Locally advanced disease</th>
<th>Metastatic disease</th>
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<tbody>
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<td>Low risk</td>
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<td>Metastatic disease</td>
<td>ADT</td>
<td>Abiraterone</td>
<td>Docetaxel</td>
<td>Enzalutamide</td>
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<td>Castration-resistant (first line)</td>
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<td>Radium-223</td>
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<td>Second line (post-docetaxel)</td>
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<td>Cabazitaxel</td>
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Options listed in alphabetical order.
ADT, androgen deprivation therapy.

neoadjuvant and adjuvant hormone treatment

The value of neoadjuvant ADT, at least in men with high-risk localised and locally advanced disease, has been established by multiple randomised trials. For example, in the Trans-Tasman Radiation Oncology Group (TROG) 96-01 trial, 818 men with locally advanced prostate cancer were randomly assigned to RT alone, RT plus 3 months neoadjuvant and concurrent combined androgen blockade (CAB) or RT plus 6 months CAB [16]. Compared with RT alone, the use of 6 months hormone therapy significantly improved overall mortality [HR 0.63 (0.48–0.83)]. Similarly, the Radiation Therapy Oncology Group (RTOG) trial 8610, in 456 men with T2–4 disease, found an improvement in 10-year prostate cancer-specific mortality (23% versus 36%; P = 0.01) with the addition of 4 months neoadjuvant and concurrent ADT to RT [17].

Adjunct ADT, after RT, has also been studied in multiple phase III trials. The RTOG 92-02 trial randomised 1,554 patients between 4 and 28 months of ADT in addition to RT [18]. In an unplanned subgroup analysis, the addition of adjuvant ADT improved overall survival in those with a Gleason score of 8–10 (81.0% versus 70.7%, P = 0.044). The European Organisation for Research and Treatment of Cancer (EORTC) 22961 trial randomised 970 men with locally advanced disease between 6 and 36 months of ADT in addition to radical RT [19]. The 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively (HR 1.42; 95% CI 1.09–1.85).

recommendations

- Neoadjuvant and concurrent ADT for 4–6 months are recommended for men receiving radical RT for high-risk disease, and should be considered for men with intermediate-risk disease [I, A].
- Adjunct ADT, for 2–3 years, is recommended for men receiving neoadjuvant hormonal therapy and radical RT, who are at high risk of prostate cancer mortality [I, A].

post-operative radiotherapy

Three randomised trials, EORTC 22911, Southwest Oncology Group (SWOG) 8794 and ARO 96-02, have compared post-operative radiotherapy versus observation after RP in patients with locally advanced disease [20–22]. Each trial has shown an advantage to post-operative radiotherapy in terms of PSA failure, but the impact on overall survival is less clear. SWOG 8794 reported after 198 deaths that overall survival was improved with adjuvant RT (HR 0.72; 95% CI 0.5–0.96; P = 0.023). However, EORTC 22911, based on 245 events found no overall survival benefit (10-year overall survival 76.9% for adjuvant radiation versus 80.7% for observation).

RT to the prostate bed has a risk of adverse effects on urinary, bowel and sexual function. For example, the SWOG 8794 trial [21] reported urethral strictures in 17.8% of men randomised to adjuvant RT versus 9.5% in those randomised to observation [response rate (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 post-operative radiotherapy after RP is not routinely recommended. Patients with positive surgical margins or extra-capsular extension after RP, with undetectable serum PSA, should be informed about the pros and cons of adjuvant RT [I, A].

treatment of relapse after radical therapy
There are no randomised trials comparing salvage RT versus observation in men with PSA failure after RP. A retrospective analysis of men with PSA failure after surgery compared the long-term outcome of those managed by observation (n = 397), with those managed by salvage RT (n = 160) [23]. Salvage radiotherapy was associated with a significant reduction in prostate cancer mortality (HR 0.32; 95% CI 0.19–0.54; P < 0.001).

recommendation
• Following RP, patients should have their serum PSA level monitored. Salvage RT to the prostate bed is recommended in the event of PSA failure. Salvage RT should start early (e.g. PSA <0.5 ng/ml) [III, B].

ADT for relapse following RP or RT has been evaluated in retrospective series. The use of early ADT was associated with a delay in time to progression but no impact on overall survival [24]. Intermittent versus continuous ADT was studied in a randomised trial of 1386 patients with a PSA at relapse of >3.0 ng/ml more than one year after RT. This study showed that intermittent therapy had a more favourable toxicity profile but no difference in overall survival (HR 1.02; 95% CI 0.86–1.21) [25].

recommendations
• Early ADT is not routinely recommended for men with biochemical relapse unless they have symptomatic local disease, or proven metastases, or a PSA doubling time <3 months [IV, B].
• Intermittent ADT is recommended for men with biochemical relapse after radical RT starting ADT [I, B].

management of advanced/metastatic disease
SWOG 9346 randomised over 1500 patients, with metastatic disease who achieved a PSA value <4 ng/ml on ADT, between intermittent and continuous ADT. The overall survival results failed to demonstrate that intermittent treatment was non-inferior to continuous ADT (HR 1.10; 90% CI 0.99–1.23) [26].

Multiple phase III trials have studied the addition of an androgen receptor (AR) antagonist to ADT alone for initial treatment of metastatic disease. Meta-analysis of trials testing a non-steroidal AR antagonist found an overall survival advantage (27.6% versus 24.7%, P = 0.005) [27]. This modest benefit is typically considered insufficient to justify combination treatment.

Three phase III trials have compared ADT alone versus ADT plus docetaxel in men with metastatic, hormone-naïve disease. Based on 237 events, the CHAARTED trial found that docetaxel improved overall survival (HR 0.61, 95% CI 0.47–0.80) [28]. The effect size was consistent across all subgroups. For example, the HR for overall survival was 0.63 (0.45–0.81) for men with high-volume disease, and 0.63 (0.34–1.17) for those with low-volume disease. GETUG-15, based on 176 events, found a similar progression-free survival but no survival difference (HR 1.01; 95% CI 0.76–1.25) [29]. STAMPEDE was a larger trial with over 2000 patients and confirmed both progression-free and overall survival benefit for adding docetaxel to ADT [30].

recommendations
• Continuous ADT is recommended as first-line treatment of metastatic, hormone-naïve disease [I, A].
• Men starting ADT should be informed that regular exercise reduces fatigue and improves quality of life [31] [I, A].
• ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy [I, A].

treatment of castrate-resistant prostate cancer
Corticosteroids decrease adrenal production of androgens and lead to favourable biochemical and clinical responses. Dexamethasone appears to be more active than prednisolone [32]. The value of corticosteroids and other hormonal manipulations, which do not have a proven overall survival benefit, has not been established by randomised trials. The arguments for their use are their favourable cost profile and, for some of these agents, their low toxicity.

The COU-302 trial tested the use of abiraterone acetate plus prednisone versus placebo plus prednisone, in over 1000 men with chemotherapy-naïve, asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (CRPC) [33]. Abiraterone improved overall survival (HR 0.79; 95% CI 0.66–0.95). The main specific side-effects were hypokalaemia, hypertension, oedema and cardiac events.

Enzalutamide was tested against placebo in the same setting in the PREVAIL trial [34]. Enzalutamide improved overall survival (HR 0.71; 95% CI 0.60–0.84). The main side-effects of enzalutamide were fatigue/asthenia and hypertension.

Sipuleucel-T, an immunotherapy using activated autologous dendritic cells, was tested against ‘placebo’ [leucopheresis was done three times, as in the active arm, but with reinfusion of one-third of the (unactivated) antigen presenting cells] in a trial of 512 patients [35]. Overall survival favoured Sipuleucel-T (HR 0.78; 95% CI 0.61–0.98), which was well tolerated. The lack of any impact on disease response or progression, taken together with logistic considerations and cost, has limited its use.

Radium-223, a bone-targeted alpha emitter, was tested against placebo in over 900 men with bone-predominant, symptomatic CRPC [36]. Radium-223 improved overall survival (HR 0.70; 95% CI 0.58–0.83) and time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52–0.83). Side-effects of radium-223 include myelosuppression, particularly thrombocytopenia, and diarrhoea.

Docetaxel has been shown in two phase III trials to improve overall survival in men with CRPC. TAX-327 compared docetaxel against mitoxantrone in over 1000 men [37]. Overall survival favoured docetaxel (HR 0.76; 95% CI 0.62–0.94). The side-effects of docetaxel included myelosuppression, fatigue, alopecia, diarrhoea, neuropathy and peripheral oedema.
**recommendations**

- Abiraterone or enzalutamide are recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC [I, A].
- Radium-223 is recommended for men with bone-predominant, symptomatic metastatic CRPC without visceral metastases [I, A].
- Docetaxel is recommended for men with metastatic CRPC [I, A].
- Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC [II, B].

The optimal sequence or combination of these agents (abiraterone, enzalutamide, radium-223, docetaxel and Sipuleucel-T) is unknown. In practice, sequencing decisions will be made in the light of the distribution, extent and pace of disease, co-morbidities, patient preferences and drug availability.

TROPIC tested cabazitaxel against mitoxantrone in 755 patients in the post-docetaxel setting [38]. Cabazitaxel improved overall survival (HR 0.70; 95% CI 0.59–0.83), but was associated with increased myelosuppression, including febrile neutropaenia and diarrhoea.

Abiraterone plus prednisone was tested against placebo plus prednisone in the post-docetaxel setting in the COU-301 trial [39]. Abiraterone improved overall survival (HR 0.74; 95% CI 0.64–0.86).

Enzalutamide was tested against placebo in the post-docetaxel setting in the AFFIRM trial, and also improved overall survival (HR 0.63; 95% CI 0.53–0.75) [40].

**recommendation**

- In patients with metastatic CRPC in the post-docetaxel setting, abiraterone, enzalutamide, cabazitaxel and radium-223 (in those without visceral disease) are recommended options [I, A].

**palliative care**

Fractionated versus single-fraction RT for bone pain has been compared in multiple randomised trials. Single-fraction treatment provides similar pain relief [41].

**recommendation**

- A single fraction of external beam RT is recommended for palliation of painful bone metastases [I, A].

Zoledronic acid, a bisphosphonate, was shown to prolong time to first skeletal-related event (SRE), namely fracture, spinal cord compression, surgery or RT for bone pain or a change in anticancer treatment [42]. However, there were no differences in disease progression, overall survival or quality of life. Adverse effects included anaemia, fever, myalgia and osteonecrosis of the jaw (ONJ). Denosumab, a RANK ligand inhibitor has been compared with zoledronate [43]. Denosumab was superior with respect to time to first SRE (HR 0.82; 95% CI 0.71–0.95, \(P = 0.0002\)), but was associated with an increased risk of hypocalcaemia (13% versus 6%) and a trend towards higher incidence of ONJ (2.3% versus 1.3%). There was no difference in overall survival. Abiraterone, enzalutamide and radium-223 all reduce the risk of SREs. The added value of zoledronate or denosumab for SRE prevention is unclear.

**recommendation**

- In patients with bone metastases from CRPC, at high risk for clinically significant SREs, denosumab or zoledronate can be recommended [I, B].

Spinal cord compression is a devastating complication of metastatic prostate cancer and early detection is critical for successful management. A systematic review found that spinal cord compression is a common finding, even in asymptomatic patients with metastatic prostate cancer and spinal metastases [44].

**recommendations**

- MRI of the spine to detect subclinical cord compression is recommended in men with CRPC with vertebral metastases [III, B].
- Urgent MRI of the spine to detect cord compression is very strongly recommended in men with CRPC with vertebral metastases and neurological symptoms [III, A].

Beta-emitting, bone seeking radionuclides such as Sr-89 and Sm-153-HEDP have proven symptomatic benefits in the treatment of metastatic CRPC. However, their use is limited by myelotoxicity and they have largely been superseded by radium-223, where this is available.

**personalised medicine**

Although there are known prognostic factors to guide management, there are no established predictive biomarkers to choose one particular treatment over another. Advanced disease progressing without a significant rise in PSA should be investigated for neuro-endocrine markers, using biopsy or blood analyses for neuron-specific enolase and/or chromogranin A [45].

**recommendation**

- Patients with evidence of neuro-endocrine change in their prostate cancer should receive chemotherapy in addition to ADT [IV, B].

**follow-up and long-term implications**

DRE has been shown to be unnecessary in men whose disease remains biochemically controlled after radical treatment [46].

**recommendations**

- Routine DRE after local therapy is not required for asymptomatic patients while the PSA remains controlled [II, B].
- Biopsy of the prostate after RT should only be carried out in men with prostate cancer who are being considered for salvage local therapy [V, C].

Men developing bowel symptoms after prostate radiotherapy may have inflammatory bowel disease, a primary colorectal malignancy or a treatable radiation enteropathy [47].

**recommendation**

- Chronic bowel symptoms after RT should be investigated by a gastroenterologist [V, B].

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**Note:**

This text is a summary of clinical practice guidelines from the Annals of Oncology. For the full text, please refer to the original publication. The guidelines provide evidence-based recommendations for the management of metastatic prostate cancer.
Table 4. Summary of recommendations

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<td>• Active surveillance is an option for men with low-risk disease [II, A].</td>
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<td>• Radical prostatectomy or radiotherapy (external beam or brachytherapy) are options for men with low- or intermediate-risk disease [I, B].</td>
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<td>• Primary ADT alone is not recommended as standard initial treatment of non-metastatic disease [III, B].</td>
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<td>• Options for patients with high-risk or locally advanced prostate cancer include external beam RT plus hormone treatment [I, B] or radical prostatectomy plus pelvic lymphadenectomy [III, B].</td>
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Continued
ADT may cause hot flushes, lethargy, mood changes, osteoporosis, insulin resistance and muscle weakness.

**Recommendation**

- Men on long-term ADT should be monitored for side-effects including osteoporosis (using bone densitometry) and metabolic syndrome [IV, B].

It is not adequate to rely on PSA alone to monitor response in men with CRPC. Rather, appropriate imaging tests should be used. However, conventional imaging techniques such as CT and bone scan do not provide assessment of response/progression in bony metastatic disease.

**Methodology**

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. A summary of recommendations is shown in Table 4. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation are shown in Table 5.
have been applied using the system shown in Table 5. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

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conflict of interest
CP has reported honoraria from Bayer, Janssen and Takeda; consultancy fees from BNIT; and research grants from Bayer. A Heidenreich has reported advisory boards of Astellas, Bayer, Dendreon, Ferring, IPSEN, Jansen and Sanofi; research grants from Astellas and Sanofi; honoraria from Amgen, Astellas, Bayer, Dendreon, Ferring, Ipsen, Jansen, Pfizer, Sanofi and Takeda. SG has reported compensated advisory boards of Bayer, Curevac, Janssen Cilag, Janssen Diagnostics, Millenium, Astellas, Novartis, Sanofi, Pfizer, Dendreon and Orion; uncompensated speakers' bureau for Amgen, Bayer, Janssen Cilag and Sanofi-Aventis; uncompensated scientific advisor for ProteoMediX. A Horwich has reported no potential conflicts of interest.

references