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European Association of Urology

Guidelines

EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer

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Abstract

Objective: To present a summary of the 2013 version of the European Association of Urology (EAU) guidelines on the treatment of advanced, relapsing, and castration-resistant prostate cancer (CRPC).

Evidence acquisition: The working panel performed a literature review of the new data (2011–2013). The guidelines were updated, and levels of evidence and/or grades of recommendation were added to the text based on a systematic review of the literature that included a search of online databases and bibliographic reviews.

Evidence synthesis: Luteinising hormone-releasing hormone (LHRH) agonists are the standard of care in metastatic prostate cancer (PCa). LHRH antagonists decrease testosterone without any testosterone surge, and they may be associated with an oncologic benefit compared with LHRH analogues. Complete androgen blockade has a small survival benefit of about 5%. Intermittent androgen deprivation results in noninferior oncologic efficacy when compared with continuous androgen-deprivation therapy (ADT) in well-selected populations. In locally advanced and metastatic PCa, early ADT does not result in a significant survival advantage when compared with delayed ADT. Relapse after local therapy is defined by prostate-specific antigen (PSA) values >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir and after radiation therapy (RT). Therapy for PSA relapse after RP includes salvage RT (SRT) at PSA levels <0.5 ng/ml and SRP or cryosurgical ablation of the prostate in radiation failures. Endorectal magnetic resonance imaging and 11C-choline positron emission tomography/computed tomography (PET/CT) are of limited importance if the PSA is <1.0 ng/ml; bone scans and CT can be omitted unless PSA is >20 ng/ml. Follow-up after ADT should include analysis of PSA and testosterone levels, and screening for cardiovascular disease and metabolic syndrome. Treatment of CRPC includes sipuleucel-T, abiraterone acetate plus prednisone (AA/P), or chemotherapy with docetaxel at 75 mg/m^2 every 3 wk. Cabazitaxel, AA/P, enzalutamide, and radium-223 are available for second-line treatment of CRPC following docetaxel. Zoledronic acid and denosumab can be used in men with CRPC and osseous metastases to prevent skeletal-related complications.

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Conclusions: The knowledge in the field of advanced, metastatic, and castration-resistant PCa is rapidly changing. These EAU guidelines on PCa summarise the most recent findings and put them into clinical practice. A full version is available at the EAU office or at www.uroweb.org.

Patient summary: We present a summary of the 2013 version of the European Association of Urology guidelines on treatment of advanced, relapsing, and castration-resistant prostate cancer (CRPC).

Luteinising hormone-releasing hormone (LHRH) agonists are the standard of care in metastatic prostate cancer (PCa). LHRH antagonists decrease testosterone without any testosterone surge, and they might be associated with an oncologic benefit compared with LHRH analogues. Complete androgen blockade has a small survival benefit of about 5%. Intermittent androgen deprivation results in noninferior oncologic efficacy when compared with continuous androgen-deprivation therapy (ADT) in well-selected populations. In locally advanced and metastatic PCa, early ADT does not result in a significant survival advantage when compared with delayed ADT. Relapse after local therapy is defined by prostate-specific antigen (PSA) values >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir and after radiation therapy. Therapy for PSA relapse after RP includes salvage radiation therapy at PSA levels <0.5 ng/ml and salvage RP or cryosurgical ablation of the prostate in radiation failures. Multiparametric magnetic resonance imaging and 11C-choline positron emission tomography/computed tomography (PET/CT) are of limited importance if the PSA is <1.0 ng/ml; bone scans, and CT can be omitted unless PSA is >20 ng/ml. Follow-up after ADT should include analysis of PSA and testosterone levels, and screening for cardiovascular disease and metabolic syndrome. Treatment of castration-resistant CRPC includes sipuleucel-T, abiraterone acetate plus prednisone (AA/P), or chemotherapy with docetaxel 75 mg/m^2 every 3 wk. Cabazitaxel, AA/P, enzalutamide, and radium-223 are available for second-line treatment of CRPC following docetaxel. Zoledronic acid and denosumab can be used in men with CRPC and osseous metastases to prevent skeletal-related complications.

The guidelines reported should be adhered to in daily routine to improve the quality of care in PCa patients. As we have shown recently, guideline compliance is only in the area of 30–40%.

1. Introduction

The most recent summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2011 [1]. This paper summarises the 2013 update of the EAU guidelines on the treatment of advanced, relapsing, and castration-resistant PCa (CRPC). The guidelines on screening, diagnosis, and treatment of clinically localised PCa were published in a separate paper. To facilitate evaluating the quality of the information provided, evidence levels and grade of recommendation have been inserted according to the general principles of evidence-based medicine [2].

2. Hormonal therapy

2.1. Luteinising hormone-releasing hormone: analogues and antagonists

Luteinising hormone-releasing hormone (LHRH) agonists have become the standard of care in hormonal therapy because these agents have the potential of reversibility and enable the use of intermittent androgen-deprivation therapy (ADT), avoid the physical and psychological discomfort associated with orchiectomy, have a lower risk of cardiotoxicity than observed with diethylstilbestrol, and result in equivalent oncologic efficacy [3,4].

In contrast to the agonists, LHRH antagonists result in a rapid decrease in luteinising hormone, follicle-stimulating hormone, and testosterone levels without any flare. In a recent prospective randomised phase 3 trial, 610 men with PCa requiring ADT were randomised to receive degarelix or leuprolide for 12 mo [5]. At the end of the observation period, degarelix was not inferior to leuprolide but achieved a more rapid suppression of testosterone within the first 3 d and avoided any flare phenomenon. In an additional analysis of secondary end points, a significantly lower risk of prostate-specific antigen (PSA) progression and PCa-specific death in favour of degarelix was described for patients with advanced disease and high baseline PSA levels [6]. However, only 11% of the patients treated with leuprolide have received flare protection with bicalutamide, and the number of patients included in the subgroup analysis is too small to draw any clinically relevant conclusions. The positive data of the C21 trial were maintained in a phase 3 extension trial where 385 patients of the C21 trial either were kept on degarelix or were switched from leuprolide to degarelix [7]. Switching from leuprolide to degarelix resulted in a significant decrease of the PSA progression-free survival (PFS) hazard rate from 0.20 events during year 1 to 0.08 events annually thereafter (chi-square test $p = 0.003$). Also, in patients with PSA >20 ng/ml at the initiation of treatment, a significant decrease of PSA PFS hazard rate from 0.38 events annually to 0.19 events annually was achieved after the switch (chi-square test $p = 0.031$).

The rapid and effective castration of LHRH antagonists primarily plays an important role in patients with

symptomatic locally advanced or metastatic disease. Its benefit in other clinical situations remains to be proven.

2.2. Antiandrogens

Both nonsteroidal antiandrogens, nilutamide and flutamide, have produced conflicting results so these agents do not play a clinically important role in the hormonal treatment of PCa as monotherapy.

As primary antiandrogen monotherapy, bicalutamide 150 mg/d was compared with medical or surgical castration in two large prospective randomised trials with identical study design including a total of 1435 patients with locally advanced M0 or M1 PCa [8]. A pooled analysis showed a significant improvement in overall survival (OS) with castration [9] in M1 patients. In M0 patients (n = 480), no significant difference was noted in OS based on the Kaplan-Meier test, but median survival was lower in the bicalutamide arm at 63.5 mo compared with 69.9 mo in the castration arm [10].

In conclusion, monotherapy with high-dose bicalutamide may be an option in locally advanced or M0 PCa patients with low PSA serum concentrations. The clinical benefits, however, remain marginal, if any, and therefore monotherapy with bicalutamide does not represent the recommended standard of care. Table 1 summarises the current indications for androgen deprivation.

2.3. Maximum androgen blockade

From the most recent systematic reviews and meta-analyses, it appears that at a follow-up of 5 yr, maximum androgen blockage (MAB) with nonsteroidal antiandrogens provides a small but statistically significant survival advantage (<5%) compared with LHRH monotherapy [11,12]. However, it has to be recognised that patients under MAB experience a significant impairment of quality of life (QoL) in the terms of sexuality, cognitive function, and thermoregulation (level of evidence [LE]: 3) [13].

2.4. Intermittent androgen deprivation

Intermittent androgen deprivation (IAD) alternates androgen blockade with treatment cessation to allow hormonal recovery between treatment cycles, thus potentially improving tolerability and QoL [14]. Patients on IAD experience improved bone health, less metabolic and haematologic disturbances, and fewer hot flashes, as well as improved sexual function. Several phase 3 trials have demonstrated the noninferiority of IAD compared with combined androgen blockade (CAB) in metastatic or biochemically recurrent disease (LE: 1b). The largest trial, SWOG 9346, randomised 1134 men with stage D2 PCa to intermittent and continuous ADT after 7 mo of induction ADT with PSA reduction <4 ng/ml [15]. PSA reductions to <0.2 ng/ml, <4 ng/ml, and >4 ng/ml were identified as significant prognostic cut-off points with regard to median survival, achieving 75 mo, 44 mo, and 13 mo, respectively. A total of 3040 were recruited, and 1535 patients (50.5%) were randomised once they decreased their PSA serum concentrations to <4 ng/ml after a 7-mo induction period with MAB [16]. After a median follow-up of 9.8 yr, median survival was 5.8 yr and 5.1 yr in the continuous and the intermittent arm, respectively. Despite the difference in

Table 1 – Indications for hormonal therapy in metastatic patients

Hormonal therapy Indications for castration	Benefits	LE
• M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathologic fractures, ureteral obstruction, extraskeletal metastasis).	1b
	Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence.	1
• M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression–related complications.	1b
	An active clinical surveillance protocol might be an acceptable option in clearly informed patients if survival is the main objective.	3
Antiandrogens		
• Short-term administration	To reduce the risk of the flare-up phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	1b
	It may be sufficient to give an antiandrogen for 3 wk of concomitant use, starting treatment on the same day as LHRH analogue treatment is started, or for up to 7 d before the first LHRH analogue injection.	4
• Long-term administration	This is an option in highly selected and motivated patients with a low PSA.	3
Intermittent androgen deprivation		
Threshold to start and stop ADT	The threshold is empirically chosen. However, it should reproduce what has been used in clinical trials. In trials, treatment is usually stopped when the PSA level is <4 ng/ml (M1) and <0.5–4 ng/ml (relapsing).	4
	Treatment is usually restarted when the PSA is >4–10 (relapsing) and >10–15 ng/ml (M1).	
Drug	LHRH analogue plus flare-up prevention *or* combined treatment.	1
Population	Metastatic patients: asymptomatic, motivated, with a clear PSA response after the induction period.	2
	Relapsing after radiotherapy: patients with a clear response after the induction period.	1b

ADT = androgen-deprivation therapy; LE = level of evidence; LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen.

survival, the statistical data are inconclusive. In patients with metastatic hormone-sensitive PCa, the confidence interval for survival exceeded the upper boundary for noninferiority, suggesting that we cannot rule out a 20% greater risk of death with intermittent therapy than with continuous therapy, but too few events occurred to rule out the significant inferiority of intermittent therapy.

In another prospective randomised clinical phase 3 trial of the SEUG, 1045 men with locally advanced or metastatic PCa were recruited, and 918 (87.8%) were randomised once the PSA serum levels decreased to <4 ng/ml after an induction period of 3 mo [17]. OS was similar between groups ($p = 0.25$), and noninferiority of IHT was demonstrated (hazard ratio [HR]: 0.90; 95% confidence interval [CI], 0.76–1.07).

In another small trial comprising 100 men with PSA progression following local treatment, the duration of the first off-treatment interval of <40 wk was associated with a significantly shorter time to development of CRPC (HR: 2.9; $p = 0.03$) and an increased PCa-specific death rate (HR: 3.8; $p = 0.04$) [18]. In another noninferiority trial, the oncologic efficacy of IAD versus continuous androgen deprivation (CAD) was analysed in a cohort of 1386 men with a PSA progression >3 ng/ml after primary or salvage radiation therapy (SRT) to the prostate [19]. Median follow-up was 6.9 yr, and there were 268 deaths in the intermittent-therapy group and 256 in the continuous-therapy group. IAD provided potential benefits with respect to physical function, fatigue, urinary problems, hot flashes, libido, and erectile function. Median OS was 8.8 yr in the intermittent-therapy group versus 9.1 yr in the continuous-therapy group (HR for death: 1.02; 95% CI, 0.86–1.21).

Data of oncologic equivalence in efficacy were reported from a prospective randomised trial including 478 patients with M1 (40%) or N+ (N1–3) disease [20]. After a median follow-up of 50.5 mo, no significant difference was observed in the median PFS (16.6 mo in IAD compared with 11.5 mo in CAB; $p = 0.17$), neither in the entire population nor in the N+ or M1 populations. The SEUG trial based on 766 patients and a mean follow-up of 55 mo observed the same lack of survival difference or overall QoL benefit in the IAD group [21]. In another prospective randomised clinical phase 3 trial, the SEUG group recruited 1045 men with locally advanced and M1 PCa but PSA serum concentrations <100 ng/ml of whom 918 men (87.8%) could be randomised [17]. After a median follow-up of 66 mo, 168 and 131 men progressed in the intermittent and in the continuous arm, respectively (HR: 1.16; 95% CI, 0.93–1.47; $p = 0.20$), but there was no significant difference in OS with 258 and 267 patients having died in the intermittent and the continuous arm, respectively.

Quite recently, Sciarra et al. [22] critically reviewed the outcome of seven prospective randomised trials randomising 4675 patients to IAD versus CAD. The induction periods ranged from 3 to 8 mo, the PSA level designated to stop ADT and to randomise patients was <4 ng/ml, and the median follow-up ranged from 40 to 108 mo. Collectively, these trials support the concept that, mainly in metastatic cases, IAD can produce oncologic results similar to CAD. In terms of overall survival, the HRs for IAD and CAD were very similar (range: 0.98–1.08).

It must be acknowledged that, so far, the thresholds at which ADT must be stopped or resumed are empirical [14,21]. Nevertheless, several points are clear [20]:

- IAD is based on intermittent castration, and therefore only drugs leading to castration should be considered.
- The initial (induction) cycle must last between 6 and 9 mo.
- The treatment is stopped only if patients have a clear PSA response, empirically defined as a PSA level <4 ng/ml in metastatic patients or <0.5 ng/ml in relapsing patients.
- The treatment is resumed when there is either clinical progression or the PSA value rises above an empirically fixed threshold (usually 4 ng/ml in nonmetastatic and 10–15 ng/ml in metastatic situations). Treatment is continued as in the induction cycle, for between 6 and 9 mo, depending on the time required to reach a PSA nadir.
- A strict follow-up must be applied, with clinical examination every 3–6 mo, with PSA measurements performed at the same time and always by the same laboratory.

In conclusion, IAD is currently widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational (LE: 1b).

2.5. *Immediate versus deferred androgen deprivation*

The most appropriate time to introduce hormonal therapy in patients with advanced PCa remains controversial. According to the European Organisation for Research and Treatment of Cancer (EORTC) 30891 trial, immediate ADT for locally advanced asymptomatic disease in men not amenable for local therapy only had a positive impact on PFS, but it did not favourably influence specific survival and QoL [23]. In a subanalysis of this trial, however, it was demonstrated that patients with an initial PSA >50 ng/ml and/or a PSA doubling time (PSA DT) <12 mo harbour a high risk of dying of PCa and might therefore be good candidates for immediate ADT to prevent or to delay complications from progressive disease [24]. However, survival is significantly better when compared with the group of patients with delayed ADT until symptoms due to progressive disease occurred. In a similar approach, the EORTC 30846 trial randomised 235 men with lymph node–positive PCa, but no local treatment to early versus delayed ADT by medical or surgical castration [25]. After a median follow-up of 13.4 yr, the 10-yr cumulative incidence of PCa-specific death was similar between both groups (55.6% and 52.1% in the delayed and the immediate group, respectively). However, the trial was too underpowered (early closure) to be able to make reliable clinical conclusions.

With regard to PSA rise after radical prostatectomy (RP), no prospective randomised clinical trials are available. Only one retrospective analysis of 1352 patients with rising PSA after RP is available for analysis [26]. Of these 1352 men, 355 started ADT at different PSA serum levels, and 997

Table 2 – Guidelines for follow-up after hormonal therapy

Recommendation	GR
• Patients should first be evaluated at 3 and 6 mo after the initiation of treatment.	B
• As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and careful evaluation of symptoms to assess treatment response and side effects.	A
• If patients undergo IAD, PSA and testosterone should be monitored in 3-mo intervals during the treatment pause.	C
• Follow-up should be tailored for the individual patient according to symptoms, prognostic factors, and the treatment given.	C
• In patients with stage M0 disease and a good treatment response, follow-up is scheduled every 6 mo and should include (as a minimum) a disease-specific history, DRE, and serum PSA determination.	C
• In patients with stage M1 disease and a good treatment response, follow-up is scheduled every 3–6 mo. As a minimum, this should include a disease-specific history, DRE, and serum PSA determination, and it is frequently supplemented with measurements of haemoglobin, serum creatinine, and alkaline phosphatise. The testosterone serum level should be checked, especially during the first year.	C
• Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
• When disease progression occurs, or if the patient does not respond to the treatment given, follow-up needs to be individualised.	C
In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient is castrated (at least testosterone <1.7 nmol/l).	A
• Routine imaging of stable patients is not recommended.	B

CRPC = castration-resistant prostate cancer; DRE = digital rectal examination; GR = grade of recommendation; IAD = intermittent androgen deprivation; PSA = prostate-specific antigen.

remained without hormonal manipulation until the detection of metastatic disease. Early ADT improved the bone metastasis–free interval only for patients with a Gleason score >7 or a PSA DT <12 mo; there was no statistically significant difference in OS or cancer-specific survival (CSS).

Since 2002, the level 1 evidence suggesting immediate ADT in every pN+ patient following RP has been questioned [27]. An analysis of 719 patients from the Surveillance Epidemiology and End Results, part of the US National Cancer Institute) database questioned the real impact of immediate ADT in pN+ patients after RP [28].

Based on a systematic review of the literature, no final recommendation can be made on the timing of hormonal therapy in advanced asymptomatic PCa.

2.6. *Follow-up of patients with prostate cancer*

During long-term therapy, ADT reduces bone mineral density (BMD) and increases the risk of fractures [29]. In the absence of associated risk factors, it is recommended that BMD be measured regularly. Based on the initial T-score [30] (LE: 3), various treatment options can be offered.

Limited information is available about the optimal level of testosterone necessary to achieve in the treatment of PCa [31]. Recent studies have suggested that lower testosterone levels may be associated with improved outcomes. In a study of 73 men with nonmetastatic PCa treated with LHRH androgen suppression [32], patients experiencing testosterone breakthroughs had a reduced biochemical recurrence-free survival rate (BCR-FS). The mean survival without androgen-independent progression in patients with testosterone breakthroughs (increase >32 ng/dl) was 88 mo (95% CI, 55–21) versus 137 mo (95% CI, 104–170) in those without breakthrough increases ($p < 0.03$).

In a retrospective series of 129 men with metastatic PCa treated with LHRH agonists, the risk of death was significantly correlated to the Gleason score ($p = 0.01$), the PSA level at 6 mo ($p = 0.01$), and the serum testosterone level at 6 mo (HR: 1.32; $p < 0.05$) [33]. Although this retrospective analysis demonstrated a significant correlation between serum testosterone at 6 mo, it remains unclear why only about 70% decreased their testosterone levels below 50 ng/dl because in many previous studies about 97% of the patients lowered the testosterone below 50 ng/dl.

In view of these findings, the measurement of serum testosterone levels, as well as serum PSA levels, should be considered part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. The first evaluation of testosterone level can be recommended at 4 wk after initiating LHRH therapy to check the nadir testosterone level achieved before readministration of the agonist drug. A 6-mo assessment of the testosterone level might be performed to evaluate the effectiveness of treatment and to ensure the castration level is being maintained. If this is not the case, switching to another type of LHRH analogue, LHRH antagonist, surgical orchiectomy, or addition of an antiandrogen can be attempted.

In patients with rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

Routine imaging procedures in stable patients are not recommended and should only be used in specific situations. Table 2 summarises the guidelines for follow-up procedures after hormonal therapy.

Besides oncologic follow-up, urologists have to screen patients for the development of metabolic sequelae associated with ADT such as alterations in lipid profiles and decreased insulin sensitivity [34]. Although little is known about the optimal strategy to mitigate the adverse metabolic effects, the Working Group recommends an emphasis on existing treatment strategies to reduce the risk of diabetes and cardiovascular disease [35]. Long-term ADT also induces osteopenia and osteoporosis so men need to be followed regularly by the measurement of BMD, serum vitamin D, and calcium levels. The antiresorptive drugs should be used in men with a BMD T-score less than −2.5 and one risk factor or more, or with hip and vertebral fractures.

Table 3 – Guidelines on treatment options for prostate-specific antigen relapse following local treatment

Recommendations	GR
• Local recurrences are best treated by salvage RT with 64–66 Gy at a PSA serum level ≤0.5 ng/ml.	B
• Expectant management is an option for patients with presumed local recurrence who are too unfit or unwilling to undergo RT.	B
• PSA recurrence indicative of systemic relapse is best treated by early ADT, resulting in decreased frequency of clinical metastases if poor prognostic risk factors such as PSA DT <12 mo or Gleason score 8–10 are present.	B
• Luteinising hormone-releasing hormone analogues/antagonists/orchiectomy or bicalutamide 150 mg/d when hormonal therapy is indicated.	A
Local recurrences can be treated with salvage RP in carefully selected patients, who presumably have organ-confined disease, that is, PSA <10 ng/mL, PSA DT >12 mo, low-dose brachytherapy, biopsy Gleason score <7.	B
Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery.	B
HIFU may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality due to the short follow-up periods reported.	B
In patients with presumed systemic relapse, ADT may be offered.	C

ADT = androgen deprivation therapy; GR = grade of recommendation; HIFU = high-intensity focused ultrasound; PSA DT = prostate-specific antigen doubling time; RP = radical prostatectomy; RT = radiation therapy.

3. Diagnosis and treatment of relapse after curative therapies

3.1. Definition of recurrence

Following RP, a confirmed PSA value >0.2 ng/ml (ie, two consecutive increases) represents recurrent cancer [36]. Following RT, a PSA value of 2 ng/ml above the nadir after RT represents recurrent cancer (Phoenix classification [37]).

Local failure following RP might be predicted with an 80% probability by a PSA increase >3 yr after RP, a PSA DT >11 mo, a Gleason score <7, and stage ≤pT3a pN0, pTx R1. Systemic failure following RP might be predicted with >80% accuracy by a PSA increase <1 yr after RP, a PSA DT of 4–6 mo, a Gleason score of 8–10, and stage pT3b, pTxpN1. In a cohort of 148 men with rising PSA and a PSA DT <12 mo following local treatment, the PFS was associated with Gleason grade ($p = 0.006$), PSA at time of treatment ($p < 0.001$), and PSA DT ($p < 0.001$) [38]. The median PFS was 19 mo, with a 3- and 5-yr metastasis PFS of 32% and 16%, respectively.

Prostatic biopsy after RT is necessary only if local procedures such as SRP are indicated in an individual patient. Treatment can then be guided by the presumed site of failure, the patient's general condition, and personal preferences (Table 3; sect. 3.2).

Imaging studies such as bone scintigraphy or computed tomography (CT) to determine the site of recurrence are of no additional diagnostic value with a positive finding in <5% unless the PSA serum levels are >20 ng/ml or the PSA velocity is >2 ng/ml per year [39,40]. Endorectal coil imaging might represent a useful technique to detect local recurrences after RP if PSA serum levels exceed 2 ng/ml [41]. Similar data were achieved in a cohort of 64 patients with PSA progression following external-beam radiation therapy (EBRT) [42]. The diagnostic accuracy to detect locally recurrent PCa was highest at a PSA level >2 ng/ml but only for 18F-choline PET/CT.

Positron emission tomography (PET) has been used successfully in many human cancers for early identification of local, locoregional, or systemic recurrences. In PCa, there are few, even if promising, published data on the clinical efficacy of PET in detecting local recurrences after RP, especially when an increased PSA value >1.0 ng/ml is detected [42,43]. As reported by Giovacchini et al. [44] in 2012, the accuracy of PET correlates with PSA values, PSA DT, and other pathologic features. A PSA DT <3 mo can certainly be regarded as a strong predictor of PET positivity as does a PSA serum level >1.5 ng/ml. In addition, imaging studies such as 11C-choline PET/CT should only be performed if therapeutic consequences such as salvage lymphadenectomy, SRP, or salvage RT to lymph nodes are being considered as a therapeutic option.

3.2. Management of prostate-specific antigen relapse following radical prostatectomy

There have been many studies on the use of RT for PSA-only recurrence following RP. As confirmed by various studies, the preradiation PSA level is critically important for optimal treatment results. Stephenson et al. [45] identified a significant relationship between PSA serum concentration at the time of RT and therapeutic outcome. The 6-yr BCR-FS was 48% in men with PSA <0.5 ng/ml, whereas it was only 40%, 28%, and 18% in men with PSA levels of 0.51–1 ng/ml, 1.01–1.5 ng/ml, and >1.5 ng/ml, respectively.

In a subanalysis of the SWOG 8974 trial, Swanson et al. [46] showed that men in all categories of post-RP PSA level (<0.2, 0.2–1.0, >1.0 ng/ml) showed an improvement with SRT in metastasis-free survival. However, the therapeutic benefit was most evident in the presence of minimal PSA serum levels. Even in men with PSA DT ≤6 mo, SRT has been reported to improve PCa-specific survival if it is given within 2 yr following a rise in the PSA level [47].

Currently, local recurrences after RP are best treated by SRT with 64–66 Gy at a PSA serum level ≤0.5 ng/ml. Siegmann et al. tried to define "what is the best time to treat" in 301 patients with biochemical recurrences after RP by evaluating the biochemical response to SRT and with a median follow-up of 30 mo [48]. In the multivariate logistic regression analysis evaluating factors influencing an undetectable PSA following SRT, only the pre-SRT PSA level (odds ratio [OR]: 2.62; $p = 0.001$) and infiltration of the seminal vesicles (OR: 2.53; $p = 0.02$) were found to be

independent predictive factors. The authors found that patients with a PSA level <0.28 ng/ml before SRT had a better outcome than those with higher PSA levels and that they may have a chance of a long-term durable response without further treatment. This approach has been validated by another group evaluating the oncologic outcome of early SRT [49].

It is still controversial whether or not the boundaries of SRT should be extended to include the pelvic lymph nodes. A significantly increased risk of PSA failure rate following SRT depending on the Roach formula was reported in a cohort of 258 men [50]. Biochemical failure at 5 yr was 0% in patients with <15% probability of lymph node metastases compared with 42% in patients with >15% probability. Adjuvant RT added to adjuvant ADT in men with positive lymph nodes following RP and extended pelvic lymphadenectomy significantly improved CSS compared with ADT alone [51]. However, this retrospective analysis in 250 patients only underlines that optimal local cancer control is essential for good long-term results.

3.3. Management of prostate-specific antigen failures after RT

In a recent review of the data of the Cancer of the Prostate Strategic Urologic Research Endeavour comprising 5277 patients with PCa, Agarwal et al. [52] demonstrated that 93% of patients who had initially been irradiated received ADT for secondary treatment of PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 yr.

Alternative therapeutic options in these patients are SRP, cryotherapy, high-intensity focused ultrasound (HIFU), and interstitial RT [53–60].

Data was reported in 2010 on the oncologic and functional outcome of patients who underwent radical salvage therapy for locally recurrent PCa after various types of modern state-of-the-art RT, performed in or after the year 2000 [53]. Overall, 40 patients (72.7%) and 15 patients (27.3%) demonstrated organ-confined and locally advanced PCa, respectively. On multivariate analysis, significant predictors of organ-confined PCa with negative surgical margins were biopsy Gleason score prior to SRP <7 ($p = 0.02$), <50% positive biopsy cores ($p = 0.001$), PSA DT >12 mo ($p = 0.001$), and low-dose brachytherapy ($p = 0.001$).

In a systematic review of the literature in 2012, Chade et al. showed that SRP allowed 5-yr and 10-yr BCR-FS estimates ranging from 47% to 82% and from 28% to 53%, respectively [54]. The 10-yr CSS and OS rates ranged from 70% to 83% and from 54% to 89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS. The authors also highlighted that the associated surgical morbidities were acceptable in the hands of experienced surgeons.

In general, SRP should only be considered in patients with a low comorbidity, a life expectancy of at least 10 yr, an organ-confined PCa ≤T2, Gleason score ≤7, and presurgical PSA <10 ng/ml.

3.4. Salvage cryosurgical ablation of the prostate for radiation failures

High-intensity focused ultrasound (HIFU) or salvage cryosurgical ablation of the prostate (CSAP) have been proposed as an alternative to SRP because both have the potential advantage of less morbidity but equal efficacy. In a recent study, the 5-yr BCR-FS was only 50% in a cohort of men who underwent partial CSAP for radio-recurrent PCa [55]. In an online data registry, the outcomes of 279 patients who underwent CSAP were analysed after a median follow-up of 21.6 ± 24.9 mo [56]. The 5-yr BCR-FS was 54.5%, according to the Phoenix classification. A case-matched control study comparing SRP and CSAP was performed in men with recurrent PCa after RT [54]. The authors compared the oncologic outcomes of the two salvage treatment options after mean follow-up periods of 7.8 in the SRP group and 5.5 yr in the SCAP group. The 5-yr BCR-free survival was 61% following SRP, significantly better than the 21% detected after CSAP. The 5-yr OS was also significantly higher in the SRP group (95% vs 85%). However, CSAP remains a therapeutic option in men with locally recurrent PCa following RT who are not suitable for or who refuse radical salvage prostatectomy

Considering HIFU, the largest cohort is based on 290 patients with a mean follow-up of 48 mo. The CSS and metastasis-free survival rates at 7 yr were 80% and 79.6%, respectively [55]. It has to be considered, however, that 163 men required ADT.

Murat et al. [59] evaluated the safety and efficacy of salvage HIFU in 167 patients with local PCa recurrence after EBRT and assessed prognostic factors for optimal patient selection. The actuarial 3-yr PFS rates were significantly lower in the case of high pre-EBRT stage (with estimates as low as 53%, 42%, and 25% for low-risk, intermediate-risk, and high-risk patients, respectively), high pre-HIFU PSA, and the use of ADT during PCa management.

Based on the poor quality of the currently available data [60], HIFU still cannot be recommended as a standard care procedure in patients with relapsing PCa after RT.

3.5. Treatment of relapse after hormonal therapy

Various different terms have been used to describe PCa that relapses after initial hormonal ablation therapy including hormone-resistant PCa (HRPC), androgen-independent cancers, and hormone-independent cancers [61,62]. The castrate-resistant, but still hormone-sensitive PCa (CRPC), has been clearly characterised, with new drugs targeting the androgen receptor (AR) (enzalutamide) or androgen synthesis (abiraterone acetate) [63]. It is important to differentiate CRPC from true HRPC. Although CRPC responds to secondary hormonal manipulations, true HRPC is resistant to all hormonal measures. Table 4 lists the key defining factors of CRPC. The definition of CRPC and the recommendations for management of patients who fail hormonal therapy are summarised in Tables 4 and 5.

Table 4 – Definition of castration-resistant prostate cancer

• Castrate serum levels of testosterone (testosterone <50 ng/dl *or* <1.7 nmol/l).
• Three consecutive rises of prostate-specific antigen (PSA), 1 wk apart, resulting in two 50% increases over the nadir with PSA >2.0 ng/ml.
• Antiandrogen withdrawal for at least 4 wk for flutamide and for at least 6 wk for bicalutamide.
• PSA progression, despite consecutive hormonal manipulations.
• Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using Response Evaluation Criteria in Solid Tumours and with nodes >2 cm in diameter.

PSA = prostate-specific antigen.

Table 5 – Recommendations for medical therapy in castration-resistant prostate cancer

Recommendations	GR
• Ideally, patients with CRPC should be counselled, managed, and treated in a multidisciplinary team.	B
• In nonmetastatic CRPC, cytotoxic therapy should only be considered in clinical trials.	B
• In patients with a rise in PSA only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	B
• Prior to treatment, PSA serum levels should be >2 ng/ml to assure correct interpretation of therapeutic efficacy.	B
• Abiraterone/prednisone should be considered in CRPC patients with asymptomatic or mildly symptomatic metastases and a low metastatic burden due to its survival benefit.	A
• In patients with metastatic CRPC and who are candidates for cytotoxic therapy, docetaxel 75 mg/m^2 every 3 wk has shown a significant survival benefit.	A
• Abiraterone/prednisone should be considered in CRPC patients who received prior docetaxel treatment as an effective second-line treatment option due to its benefit in overall survival and radiographic progression-free survival and QoL.	A
• Enzalutamide should be considered in CRPC patients as an effective second-line treatment due to its benefit in overall survival and radiographic progression-free survival and QoL.	B
• Cabazitaxel should be considered as effective second-line treatment following docetaxel.	A
• Second-line docetaxel may be considered in previously responding patients to docetaxel. Otherwise, treatment is tailored to the individual patient.	C
• Radium-223 should be considered in CRPC patients with osseous metastases due to its benefit in overall survival, QoL, and pain.	A

CRPC = castration-resistant prostate cancer; GR = grade of recommendation; PSA = prostate-specific antigen; QoL = quality of life.

It is recommended to continue ADT with LHRH analogues, despite PSA progression, based on the data of Manni et al. [64]. This idea is further supported by data from a multivariate postrandomisation Cox regression analysis of 102 men with localised unfavourable PCa who underwent RT plus 6 mo of ADT [65]. The time-to-testosterone recovery (TTR) had a significant impact on the risk of CSS ($p = 0.03$). If TTR increased to >2 yr, none of the patients died due to PCa.

3.6. Secondary hormonal therapy

Many therapeutic options are available for the patient with progressive disease following ADT. They include antiandrogen withdrawal, addition of antiandrogens, oestrogenic compounds, adrenolytic agents, and novel approaches [66]. Although many second-line treatment regimes have resulted in prolonged PFS and PSA responses, none of the approaches have resulted in an improved OS or CSS. With the new hormonal and cytotoxic agents available, the use of unspecific second-line hormonal manipulations is no longer supported, necessary, or mandatory prior to the applications of the new substances.

New promising hormonal and nonhormonal agents have been and are being evaluated in prospective randomised clinical phase 3 trials and are highlighted in the following paragraph. For practical purposes, treatment options in CRPC are divided into first-line and second-line treatment scenarios.

3.6.1. First-line treatment in castration-resistant prostate cancer

3.6.1.1. Sipuleucel-T. Sipuleucel-T (Sip-T) was approved in the United States for the treatment of asymptomatic or minimally symptomatic mCRPC patients; the drug is not approved in Europe [67]. Sip-T is an autologous vaccine consisting of individually collected antigen-presenting cells that are exposed to the fusion protein prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor and than reinfused to the patient at weeks 0, 2, and 4. In the IMPACT study, median survival with Sip-T was 25.8 mo compared with 21.7 mo with placebo, and the most frequently reported adverse events were chills, fever, and headache in the Sip-T arm. It has to be considered, however, that only patients with a good Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, asymptomatic or mildly symptomatic osseous metastases, and absence of visceral metastases were included in the trial. It has been shown recently that the baseline PSA serum level at time of trial inclusion was of significant prognostic relevance: Estimated 3-yr survival in the lowest PSA quartile was 62.6% for Sip-T patients and 41.6% for control patients, representing a 50% relative increase [68].

3.6.1.2. Abiraterone acetate plus prednisone. In 2012, the lyase inhibitor abiraterone acetate plus prednisone (Cyp 17 inhibitor) was approved for treatment of asymptomatic and mildly symptomatic metastatic CRPC (mCRPC) patients based on the results of the COU-302 trial [69]. In the COU-302 trial, 1088 men with asymptomatic or mildly

symptomatic mCRPC were randomised in a 1:1 fashion to receive either AA/P at 1000 mg/d and 5 mg twice daily, respectively, or placebo with prednisone. The primary end point was overall and radiographic PFS (rPFS) by central review. Secondary end points were PSA response, time to opiate use, time to progression, time to chemotherapy, and time to deterioration of ECOG performance status. Median OS was 35.3 mo and 27.2 mo in the AA/P and in the placebo group ($p = 0.01$), respectively [70]. But, the coprimary end point rPFS was significantly improved in the AA/P with 16.5 mo compared with 8.3 mo in the placebo arm ($p < 0.001$). On all secondary end points, AA/P resulted in significantly improved effects. Grade 3 and 4 toxicities developed in 48% and 42% of the patients in the AA/P and in the placebo arm, respectively. The most common side effects were fatigue, back pain, arthralgia, nausea, and gastrointestinal toxicities.

3.6.1.3. Docetaxel. Based on prospective randomised phase 3 trials, docetaxel at 75 mg/m^2 at 3-wk intervals in combination with prednisone represents the cytotoxic regime of choice in men with CRPC resulting in a median survival benefit of 3 mo and a significant improvement of pain and QoL compared with mitoxantrone [71]. The beneficial effect of docetaxel is independent of age, pain, or performance status at initiation, and the presence of symptomatic or asymptomatic metastatic disease. The most appropriate indication for chemotherapy might be the clinical scenario of symptomatic or extensive metastases, rapid PSA DT, high Gleason score, or short-term response to primary ADT considering the inclusion criteria of the COU-302, IMPACT, and TAX327 trial.

Several poor prognostic factors have been described, such as visceral metastases, pain, anaemia (haemoglobin < 13 g/dl), bone scan progression, and prior estramustine before docetaxel. Patients were categorised into three risk groups: good risk (zero to one factor), intermediate (two factors), and high risk (three to four factors), leading to three different median rates of OS: 25.7, 18.7, and 12.8 mo, respectively [72].

3.7. Second-line treatment in castration-resistant prostate cancer

3.7.1. Docetaxel rechallenge

Although this approach has never been tested in prospective randomised clinical trials, there is enough scientific evidence from large retrospective series to identify patients who might be good candidates for reexposure [73–76]. Patients who respond with a PSA decrease $\geq$30% maintained for at least 8 wk demonstrate a positive PSA response in about 55–60% during reexposure without increasing treatment-related toxicity although no OS survival benefit has been reported.

3.7.2. Abiraterone acetate plus prednisone

AA/P was evaluated in the clinical phase 3 prospective randomised double-blind placebo-controlled multicentre COU-301 trial versus placebo in a cohort of 1195 progressive mCRPC patients who failed docetaxel-based chemotherapy [77]. OS was the primary end point, and time to progression, PSA response, and rPFS were secondary end points of the trial. The median follow-up in the overall study population was 12.8 mo. OS was significantly improved by 3.9 mo from 10.9 mo in the placebo arm to 14.8 mo in the AA/P arm ($p < 0.001$). All secondary end points were met, and all end points demonstrated a significantly improved benefit for the AA/P group.

The profile of adverse events was similar to the COU-302 trial, and most of the side effects did not significantly differ statistically between AA/P and placebo. However, adverse events with regard to the CYP 17 blockade (fluid retention, oedema, hypokalemia, arterial hypertension), cardiac events, and elevation of liver transaminases were observed significantly more often in the AA/P arm (55% vs 43%; $p < 0.001$). Especially the frequency of fluid retention and oedema (31% vs 22%; $p = 0.04$) and hypokalemia (17% vs 8%; $p < 0.001$) developed significantly more often in the AA/P arm. The frequency of cardiac events, however, did not differ significantly between the two groups (13% vs 11%).

3.7.3. Enzalutamide (formerly MDV3100)

Enzalutamide (ENZ) is an orally administered drug that acts as an AR-signalling inhibitor and is a pure antagonist of the AR with 10 times greater affinity to the AR relative to bicalutamide [78]. The AFFIRM trial was a clinical phase 3 prospective randomised double-blind placebo-controlled trial in men with mCRPC that recruited 1199 patients who were randomised to receive ENZ at 160 mg/d or to receive placebo [79]. The primary end point was OS; secondary end points were measures of response (PSA decrease, objective remission, QoL) and measures of progression (time to PSA increase, radiographic PFS, time to first skeletal event). The median follow-up was 14.4 mo; the median treatment duration was 8.3 mo and 3.0 mo in the ENZ and the placebo arm, respectively. The median OS was 18.4 mo and 13.6 mo ($p < 0.0001$) in the ENZ and in the placebo group, respectively, with a relative risk reduction of death by 37%. All secondary end points were met with a statistically significant benefit in the ENZ arm.

With regard to safety, the ENZ group experienced fewer grade 3/4 toxicities than the placebo group (45% vs 53%). There was a higher incidence of all grades of fatigue, diarrhoea, hot flashes, musculoskeletal pain, and headache in the ENZ group without any statistically significant differences between the two groups. The risk of seizures was slightly elevated in the ENZ group with a frequency of 0.9% versus 0%.

3.7.4. Cabazitaxel plus prednisone

Cabazitaxel (CBZ) is a second-generation tubulin-binding taxane that was selected for further clinical trials based on its antitumour activity in models resistant to docetaxel and paclitaxel and its high cytotoxicity. The TROPIC trial was a prospective randomised open-label clinical phase 3 trial that recruited 755 patients with mCRPC who progressed during or after docetaxel-based chemotherapy [80]. Patients received CBS 25 mg/m^2 and prednisone 5 mg twice daily at 21-d intervals for 10 cycles or mitoxantrone

12 mg/m^2 and prednisone 5 mg twice daily at 21-d intervals for 10 cycles. The primary study end point was OS; secondary end points were PFS, PSA response rate, objective tumour response rate, pain response, and safety. CBZ plus prednisone resulted in a median OS of 15.1 mo compared with 12.7 mo for patients receiving mitoxantrone plus prednisone (HR: 0.70; 95% CI, 0.59–0.83; $p < 0.0001$). All secondary end points of the trials were reached and were in favour of CBZ (Table 5).

With regard to safety, the CBZ and prednisone group experienced significantly more grade 3/4 toxicities than the placebo group. The most common side effect to the mitoxantrone group were haematologic, and the most common grade 3/4 toxicities were neutropenia (82% vs 58%), leukopenia (68% vs 42%), and anaemia (11% vs 5%). Diarrhoea was the most common nonhaematologic side effect and occurred in 6% and <1% in the CBZ and prednisone and the mitoxantrone and prednisone group, respectively. The German Compassionate-Use Programme included 111 patients with mCRPC who met the inclusion criteria of the TROPIC trial, and the frequency of neutropenia, leukopenia, and anaemia decreased to 7.2%, 9.0%, and 4.5%, respectively [81]. Grade 3/4 gastrointestinal toxicity was observed in only 0.9% of the patients. The most likely reason for the improved toxicity profile is the experience of the investigators, guideline-compliant application of granulocyte colony-stimulating factor even at cycle 1, and preventive measures with regard to the treatment of diarrhoea.

3.8. Bone-targeting and bone-metastasis targeting agents

More than 90% of patients with CRPC have bone metastases [82]. Bone lesions are associated with elevated osteoclast activity that releases tumour-growth stimulating factors from the bone. The cycle of bone destruction and tumour growth continues, leading to skeletal-related events such as spinal cord compression, pathologic fracture, and the need for surgery or EBRT [83]. Bone metastases are a major cause of death, disability, and decreased QoL, as well as increasing cost of treatment.

To date, zoledronic acid is the only bisphosphonate that has been shown to reduce both pain and the number of skeletal-related events in CRPC patients with bone metastases compared with placebo [84].

Denosumab is a monoclonal antibody against the receptor activator of nuclear factor κ-B ligand and is licensed in the United States, United Kingdom, and Europe to treat men at risk of bone loss or fracture associated with hormonal therapy (age >70 yr with osteopenia or history of osteoporotic fracture) [85]. The median time to first on-study skeletal-related event was 20.7 mo with denosumab compared with 17.1 mo with zoledronic acid (HR: 0.82; 95% CI, 0.71–0.95; $p = 0.0002$ for noninferiority; $p = 0.008$ for superiority). There was, however, no difference in OS between the two treatment groups. In a 2012 prospective randomised double-blind placebo-controlled trial, Smith et al. [86] evaluated the therapeutic efficacy of denosumab 120 mg every 4 wk versus placebo in 1423 men with nonmetastatic CRPC and aggressive PSA kinetics defined as a PSA >8.0 ng/ml and/or a PSA DT <10 mo. The median time to first bone metastases was significantly prolonged by 4.3 mo (29.5 vs 25.2; $p = 0.028$). Bone metastases–free survival was significantly improved by 16%, 23%, and 29% in patients with a PSA DT of <10 mo, <6 mo, and < 4 mo, respectively. Rates of adverse events and serious adverse events were similar in both groups, except for osteonecrosis of the jaw and hypocalcaemia. Overall, 33 patients (5%) on denosumab developed osteonecrosis of the jaw versus none on placebo. Hypocalcaemia occurred in 12 patients (2%) on denosumab and 2 (<1%) on placebo.

Radium-223 is a radiopharmaceutical that acts as a calcium mimic and targets new bone growth in and around bone metastases via heavy α particles that have an ultra-short range <100 μm [87] that was recently approved by the Food and Drug Administration and the European Medicines Agency. It may take only a single α particle to kill a cancer cell, and the short penetration results in highly localised tumour-cell killing with minimal damage to surrounding healthy cells. In the updated analysis of the ALSYMPCA study that included 921 CRPC patients, the median OS was 14.9 mo with radium-223 compared with 11.3 mo with placebo (HR: 0.695; 95% CI, 0.581–0.8732; $p < 0.0001$) [88].

It has been shown that all of the treatment approaches just described can be applied in the elderly patient without increasing therapy-related side effects or without decreasing oncologic efficacy. However, it is recommended to adapt the therapeutic approach according to the International Society of Geriatric Oncology guidelines [89].

Currently, there is lack of evidence on a specific sequence of therapy. Therefore, physicians should adhere to the inclusion criteria of the various clinical trials when treating real-world patients with CRPC. Furthermore, the EAU guideline panel on PCa believes that any patient with PCa and especially CRPC is on a clinical trial.

3.9. Palliative therapeutic options

Many patients with CRPC have painful bone metastases and are not amenable for chemotherapy, making effective palliative treatment options necessary. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses, and social workers. Critical issues of palliation must be addressed while considering additional systemic treatment including management of pain, constipation, anorexia, nausea, fatigue, and depression (ie, palliative EBRT, cortisone, analgesics, and antiemetics).

4. Summary

The present text represents a summary. For more detailed information and a full list of references, refer to the full-text version. These EAU guidelines (ISBN 978-90-79754-71-7) are available at the EAU Web site: http://www.uroweb.org/guidelines/online-guidelines/.

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