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## SPECIAL ARTICLE

### EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer<sup>☆</sup>

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#### Abstract

**Objectives:** Our aim is to present a summary of the 2010 version of the European Association of Urology (EAU) guidelines on the treatment of advanced, relapsing, and castration-resistant prostate cancer (CRPC).

**Methods:** The working panel performed a literature review of the new data emerging from 2007 to 2010. The guidelines were updated, and the levels of evidence (LEs) and/or grades of recommendation (GR) were added to the text based on a systematic review of the literature, which included a search of online databases and bibliographic reviews.

**Results:** Luteinising hormone-releasing hormone (LHRH) agonists are the standard of care in metastatic prostate cancer (PCa). Although LHRH antagonists decrease testosterone without any testosterone surge, their clinical benefit remains to be determined. Complete androgen

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blockade has a small survival benefit of about 5%. Intermittent androgen deprivation (IAD) results in equivalent 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 after radiation therapy (RT). Therapy for PSA relapse after RP includes salvage RT at PSA levels  $<0.5$  ng/ml and salvage RP or cryosurgical ablation of the prostate in radiation failures. Endorectal magnetic resonance imaging and  $^{11}\text{C}$ -choline positron emission tomography/computed tomography (CT) are of limited importance if the PSA is  $<2.5$  ng/ml; bone scans and CT can be omitted unless PSA is  $>20$  ng/ml. Follow-up after ADT should include screening for the metabolic syndrome and an analysis of PSA and testosterone levels. Treatment of castration-resistant prostate cancer (CRPC) includes second-line hormonal therapy, novel agents, and chemotherapy with docetaxel at  $75\text{ mg/m}^2$  every 3 wk. Cabazitaxel as a second-line therapy for relapse after docetaxel might become a future option. Zoledronic acid and denusomab can be used in men with CRPC and osseous metastases to prevent skeletal-related complications.

**Conclusion:** The knowledge in the field of advanced, metastatic, and CRPC 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 online at [www.uroweb.org](http://www.uroweb.org).

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## PALABRAS CLAVE

Cáncer de próstata;  
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MDV3100;  
Abiraterona;  
Docetaxel;  
Ácido zoledrónico;  
Denusomab

## Guía de la EAU sobre el cáncer de próstata. Parte II: tratamiento del cáncer de próstata avanzado, recidivante y resistente a la castración

### Resumen

**Objetivos:** Nuestro objetivo es presentar un resumen de la guía de 2010 de la Asociación Europea de Urología (EAU) respecto al tratamiento del cáncer de próstata avanzado, recidivante y resistente a la castración (CPRC).

**Métodos:** El grupo de trabajo hizo una revisión de la literatura en relación con los nuevos datos que habían surgido entre 2007 y 2010. Se actualizó la guía y se añadieron niveles de evidencia y/o grados de recomendación al texto, basándonos en una revisión sistemática de la literatura, lo que incluyó una búsqueda de bases de datos en línea y revisiones bibliográficas.

**Resultados:** Los agonistas de la hormona liberadora de gonadotropina (LHRH) constituyen el tratamiento estándar en cáncer de próstata (CP) metastático. Aunque los agonistas de la LHRH reducen la testosterona sin que se den picos en la testosterona, sus ventajas clínicas aún están por determinar. El bloqueo androgénico total proporciona una pequeña ventaja en la supervivencia de aproximadamente el 5%. La privación intermitente de andrógenos produce una eficacia oncológica equivalente a la conseguida con la terapia de privación androgénica continua (TPA) en poblaciones bien seleccionadas. En el CP metastático y localmente avanzado, la TPA temprana no produce una ventaja significativa en términos de supervivencia en comparación con la TPA tardía. La recidiva tras la terapia local está definida por valores del antígeno prostático específico (APE)  $>0.2$  ng/ml tras la prostatectomía radical (PR) y  $>2$  ng/ml por encima del nadir tras la radioterapia (RT). La terapia para la recidiva del APE tras PR incluye RT de rescate a niveles de APE  $<0.5$  ng/ml y PR de rescate o ablación crioquirúrgica de la próstata en caso de fracaso de la radiación. La resonancia magnética endorrectal y la tomografía axial computarizada/tomografía de emisión de positrones con  $^{11}\text{C}$ -colina son de poca relevancia si el APE es  $<2.5$  ng/ml; se pueden omitir la gammagrafía ósea y la TAC, excepto cuando el APE es  $>20$  ng/ml. El seguimiento tras la TPA debe incluir el cribado del síndrome metabólico y un análisis de los niveles de APE y de testosterona. El tratamiento del cáncer de próstata resistente a la castración (CPRC) incluye tratamiento hormonal de segunda línea, nuevos fármacos y quimioterapia con  $75\text{ mg/m}^2$  de docetaxel cada tres semanas. Es posible que en el futuro se pueda emplear cabazitaxel como tratamiento de segunda línea para recidiva tras docetaxel. Pueden utilizarse ácido zoledrónico y denusomab en hombres con CPRC y metástasis óseas, a fin de prevenir complicaciones relacionadas con el esqueleto.

**Conclusión:** Está cambiando rápidamente lo que se sabe en el ámbito del CPRC avanzado y metastático. Esta guía de la EAU sobre CP resume los resultados más recientes y los sitúa en la práctica clínica.

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## Introduction

The most recent summary of the European Association of Urology (EAU) guidelines on PCa was published in 2008.<sup>1</sup> This paper summarises the 2010 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 have been published in a separate paper. To facilitate evaluating the quality of the information provided, we inserted LEs and GR according to a modified classification system from the Oxford Centre for Evidence-Based Medicine levels of evidence.<sup>2</sup>

## Hormonal therapy

### 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:

1. Have the potential for reversibility and enable the use of IAD therapy.
2. Avoid the physical and psychological discomfort associated with orchiectomy.
3. Have a lower risk of cardiotoxicity as observed with diethylstilbestrol.
4. Result in equivalent oncologic efficacy.<sup>3,4</sup>

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.<sup>5</sup> 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, PSA progression and PCa-specific death in favour of degarelix were described for patients with advanced disease and high baseline PSA levels.<sup>6</sup> However, only 11% of the patients treated with leuprolide received flare protection with bicalutamide, and the number of patients included in the subgroup analysis was too small to draw any clinically relevant conclusions.

The rapid and effective castration of LHRH antagonists plays an important role in patients with symptomatic metastatic disease (bone metastases, neurologic symptoms due to impending spinal cord compression, subvesical obstruction). Its benefit in other clinical situations remains to be proven.

### Antiandrogens

The use of steroidal antiandrogens has resulted in significantly poorer survival data when compared with goserelin. Both the 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 1435 patients with locally advanced M0 or M1 PCa.<sup>7</sup> A pooled analysis showed:

1. In M1 patients there was a significant improvement in overall survival (OS) with castration.<sup>8</sup>
2. 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.<sup>9</sup>

In conclusion, monotherapy with nonsteroidal antiandrogens may be an option with high-dose bicalutamide in locally advanced or highly selected well-informed metastatic patients (low PSA). 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.

### Maximum androgen blockade

From the most recent systematic reviews and meta-analyses, it appears that at a follow-up of 5 yr, maximum androgen blockade (MAB) with nonsteroidal antiandrogens provides a small but statistically significant survival advantage (<5%) when compared with LHRH monotherapy.<sup>10,11</sup> It remains debatable whether this small advantage can be meaningful when applied to everyday clinical practice. Furthermore, it has to be recognised that patients under MAB experience a significant impairment of quality of life (QoL) in the areas of sexuality, cognitive function, and thermoregulation (LE: 3).<sup>12</sup>

### Intermittent androgen deprivation

IAD alternates androgen blockade with treatment cessation to allow hormonal recovery between treatment cycles, thus potentially improving tolerability and QoL.<sup>13</sup> 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, Southwest Oncology Group (SWOG) 9346, randomised 1134 men with stage D2 PCa to IAD and continuous ADT after 7 mo of induction ADT with a PSA reduction <4 ng/mL.<sup>14</sup> A PSA reduction to <0.2 ng/mL, <4 ng/mL, and >4 ng/mL was identified as significant prognostic cut-off points with regard to median survival, achieving 75 mo, 44 mo, and 13 mo, respectively. These important results are the only available information from this large cohort. The formal survival comparison is awaited. 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 (hazard ratio [HR]: 2.9;  $p=0.03$ ) and an increased PCa-specific death rate (HR: 3.8;  $p=0.04$ ).<sup>15</sup>

**Table 1** Indications for hormonal therapy.

Hormonal therapy indications for castration	Benefits	LE
<i>General guidelines</i>	<p>In advanced PCa, all forms of castration used as monotherapy (e.g., orchiectomy, LHRH, diethylstilbestrol) have equivalent efficacy.</p> <p>In metastatic PCa, the addition of a nonsteroidal antiandrogen to castration (CAB) results in a small advantage in OS over castration alone but is associated with increased adverse events, reduced QoL, and high costs.</p> <p>IAD should no longer be regarded as experimental, even though long-term data from prospective clinical trials are still awaited. "Minimal" ADT, however, should continue to be seen as experimental.</p>	1
<i>M1 symptomatic</i>	<p>To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathologic fractures, ureteral obstruction, extraskelatal metastasis).</p> <p>Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence.</p> <p>LHRH antagonists might be used with rapid decrease of serum testosterone.</p>	1
<i>M1 asymptomatic</i>	<p>Immediate castration to defer progression to a symptomatic stage and prevent serious complications related to disease progression.</p> <p>An active clinical surveillance protocol might be an acceptable option in clearly informed patients if survival is not the main objective.</p>	1b 3
<i>N+</i>	<p>Immediate castration to prolong PFS and even OS.</p> <p>Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy.</p>	1b 3
<i>Locally advanced M0</i>	Immediate castration to improve cancer-free survival.	1b
<i>Locally advanced disease treated with radiotherapy</i>	Adjuvant ADT to improve cancer-free survival.	1b
<i>Localised disease treated with radiotherapy</i>	–	–

Table 1 (Continued)

Hormonal therapy indications for castration	Benefits	LE
<i>High-risk d'Amico</i>	Adjuvant ADT to improve cancer-free survival.	1b
<i>Intermediate-risk d'Amico</i>	If low dose (<75 Gy) radiotherapy: 6 mo of ADT. If high dose (>75 Gy) radiotherapy: ADT questionable.	2
<i>Locally advanced asymptomatic unfit for local definitive treatment</i>	Limited OS improvement not related to a CSS benefit. Immediate ADT to improve PFS and symptom-free survival.	1
<i>Antiandrogens</i>		
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. <sup>89,90</sup>	1b
Nonsteroidal antiandrogen monotherapy	Primary monotherapy as an alternative to castration in patients with locally advanced PCa (T3–4, any N, or any T).  No place in localised disease as a single-treatment modality.  Combined with radiotherapy: according to the EPC trial, improvement in PFS and OS in locally advanced disease.  Combined with RP: no place so far in an adjuvant setting.	2

IAD: intermittent androgen deprivation; ADT: androgen-deprivation therapy; CAB: complete androgen blockade; CSS: cancer-specific survival; EPC: Early Prostate Cancer Trialists' Group; LE: level of evidence; LHRH: luteinising hormone-releasing hormone; QoL: quality of life; OS: overall survival; PCa: prostate cancer; PFS: progression-free survival; RP: radical prostatectomy.

Data of oncologic equivalence in efficacy were reported from a prospective randomised trial including 478 patients with M1 (40%) or N+ (N1–3) disease.<sup>16</sup> After a median follow-up of 50.5 mo, no significant difference was observed in the median progression-free survival (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 population. The South European Urological Group 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.<sup>17</sup>

It must be acknowledged that, so far, the threshold at which ADT must be stopped or resumed is empirical.<sup>13,17</sup> Nevertheless, several points are clear<sup>18</sup>:

1. IAD is based on intermittent castration, and therefore only drugs leading to castration should be considered.
2. The initial (induction) cycle must last between 6 and 9 mo.
3. 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.
4. 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.
5. 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 and widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational (LE: 2).



## 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 did not favourably influence specific survival and QoL.<sup>19</sup> 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 harboured a high risk of dying of PCa and therefore might be good candidates for immediate ADT to prevent or to delay the complications from progressive disease.<sup>20</sup> However, survival was 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.<sup>21</sup> 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 reach 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.<sup>22</sup> Of these 1352 men, 355 started ADT at different PSA serum levels; 997 remained without hormonal manipulation until 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).

The Cochrane Library review extracted four good quality randomised controlled trials,<sup>23–26</sup> which were all conducted in the pre-PSA era and included patients with advanced PCa who received early versus deferred ADT as primary therapy. According to the analysis, early androgen suppression significantly reduces disease progression and complication rates due to the progression itself, but it does not improve CSS and provides a relatively small benefit in OS, with an absolute risk reduction of 5.5% that does not become evident until after 10 yr.<sup>27</sup>

Since 2002, the results of the EST3886 trial suggesting immediate ADT in every pN+ patient following RP have been questioned.<sup>28</sup> Recently, an analysis of 719 patients from the US National Cancer Institute Surveillance Epidemiology and End Results database questioned the real impact of immediate ADT in pN+ patients after RP.<sup>29</sup>

Based on a systematic review of the literature, no final recommendation can be made on the timing of hormonal therapy in advanced asymptomatic PCa.<sup>30</sup>

## Follow-up of patients with prostate cancer

During long-term therapy, ADT reduces bone mineral density (BMD) and increases the risk of fractures.<sup>31</sup> In the

absence of associated risk factors, it is recommended that BMD be regularly measured based on the initial *T* score<sup>32</sup> (LE: 3):

1. Every 2 yr, if the initial *T* score is less than  $-1.0$ .
2. Every year, if the *T* score is between  $-1.0$  and  $-2.5$ .

Limited information is available about the optimal level of testosterone necessary to achieve in the treatment of PCa.<sup>33</sup> Recent studies have suggested lower testosterone levels may be associated with improved outcomes. In a study of 73 men with nonmetastatic PCa treated with LHRH androgen suppression,<sup>34</sup> patients experiencing testosterone breakthroughs had a reduced biochemical survival rate. The mean survival without androgen-independent progression in patients with testosterone breakthroughs (increase >32 ng/dl) was 88 mo (95% confidence interval [CI], 55–121) 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 with 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;  $p < 0.05$ ).<sup>35</sup> 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 their 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 as 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 3 mo 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 LHRH agent, surgical orchiectomy, or the 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.

In addition to oncologic follow-up, urologists have to screen patients for the development of metabolic sequelae associated with ADT. Medical or surgical castration causes changes in body composition, alterations in lipid profiles, and decreased insulin sensitivity.<sup>36</sup> 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.<sup>37</sup>

**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. As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and careful evaluation of symptoms to assess treatment response and side effects.	B
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 for every 3–6 mo. As a minimum, this should include a disease-specific history, DRE, and serum PSA determination, and is frequently supplemented with measurements of haemoglobin, serum creatinine, and alkaline phosphatase.	C
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	–
When disease progression occurs or if the patient does not respond to the treatment given, follow-up needs to be individualised.	C
Routine imaging of stable patients is not recommended.	B

DRE: digital rectal examination; GR: grade of recommendation; IAD: intermittent androgen deprivation; PSA: prostate-specific antigen.

## Diagnosis and treatment of relapse after curative therapies

### Definition of recurrence

Following RP, a confirmed PSA value  $>0.2$  ng/ml (i.e., two consecutive increases) represents recurrent cancer.<sup>38</sup>

**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 $\leq 0.5$ 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/orchiectomy or bicalutamide 150 mg/d when hormonal therapy is indicated. It has to be considered, however, that bicalutamide 150 mg/d is inferior to castration in patients with M0 and M1 disease.	A
Salvage radical prostatectomy should be considered in patients with a very high probability of organ confined local recurrences. Salvage RP should be performed in experienced centres only.	B

ADT: androgen-deprivation therapy; GR: grade of recommendation; PSA: prostate specific antigen; PSA DT: prostate-specific antigen doubling time; RT: radiation therapy.

Following radiation therapy (RT), a PSA value of 2 ng/ml above the nadir after RT represents recurrent cancer.<sup>39</sup>

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  $\leq$ 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 ( $p<0.001$ ).<sup>40</sup> 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 salvage RP 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).

Imaging studies such as bone scintigraphy or computed tomography (CT) to determine the site of recurrence are of no additional diagnostic value unless the PSA serum levels are  $>20$  ng/ml or the PSA velocity is  $>2$  ng/ml per year.<sup>41–43</sup> Endorectal coil imaging might represent a useful technique to detect local recurrences after RP if PSA serum levels exceed 2 ng/ml.<sup>44</sup> Similar data were obtained in a cohort of 64 patients with PSA progression following external-beam radiation therapy (EBRT).<sup>45</sup> The diagnostic accuracy to detect locally recurrent PCa was highest at a PSA level  $>2$  ng/ml.

Positron emission tomography (PET) with  $^{11}\text{C}$ -choline is not indicated as a routine imaging study in the clinical situation of PSA rise after local treatment with curative intent.<sup>46</sup> The detection rate of  $^{11}\text{C}$ -choline PET-CT appears to depend strongly on PSA levels at the time of diagnosis, pathologic stage at time of initial diagnosis, previous biochemical failure, and older age; this was recently demonstrated in a cohort of 358 patients with PSA relapse following RP and a mean PSA level of  $3.97 \pm 6.94$  ng/ml at the time of evaluation.<sup>47,48</sup> Furthermore, the probability of false-positive results in up to 20% of patients has to be considered when interpreting PET results.<sup>49</sup>

The timing and mode of treatment of PSA-only recurrence after RP or RT remains controversial. After RP, the usually accepted therapeutic options are RT to the prostatic bed and/or pelvic lymph nodes, CAB, or IAD.

All other options that have been reported are still experimental and should be discussed individually with the patient. Ideally, the following options should be further tested in prospective clinical trials before they can be recommended as a standard treatment option:

1. Salvage pelvic lymphadenectomy or salvage metastasectomy.
2. Combination of antiandrogens with  $5\alpha$ -reductase inhibitors.
3. Early chemohormonal approaches.

These same therapeutic options in addition to EBRT may be applied to PSA recurrences following RT. In addition, salvage RP, cryotherapy, high-intensity focussed ultrasound (HIFU), or brachytherapy may be discussed in carefully selected patients.

### Management of prostate-specific antigen relapse following radical prostatectomy

Many studies have been conducted 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.<sup>50</sup> identified a significant relationship between PSA serum concentration at the time of RT and therapeutic outcome: The 6-yr biochemical-free survival 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.<sup>51</sup> 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 salvage RT 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  $\leq 6$  mo, salvage RT was reported to improve PCa-specific survival if given within 2 yr following a rise in the PSA level.<sup>52</sup>

Currently, local recurrences after RP are best treated by salvage RT with 64–66 Gy at a PSA serum level  $\leq 0.5$  ng/ml. It is still controversial whether or not the boundaries of salvage RT should be extended to include the pelvic lymph nodes. Recently, a significantly increased risk of PSA failure rate following salvage RT based on the Roach formula was reported in a cohort of 258 men.<sup>53</sup> 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.<sup>54</sup> However, this retrospective analysis in 250 patients only underlines that optimal local cancer control is essential for good long-term results.

### Management of prostate-specific antigen relapse following radical prostatectomy

In a recent review of the data of the Cancer of the Prostate Strategic Urologic Research Endeavour comprising 2336 patients with PCa, Grossfeld et al.<sup>55</sup> demonstrated that 92% 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 was approximately 3 yr.

Alternative therapeutic options in these patients are salvage RP, cryotherapy, HIFU, and interstitial RT.<sup>56–60</sup> Salvage RP has not gained widespread acceptance because of its associated morbidity, namely incontinence, local recurrences, and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

Recently, data were reported 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 2000 or after.<sup>58</sup> Forty 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 as follows:

1. Biopsy Gleason score before salvage RP  $<7$  ( $p=0.02$ ).
2.  $<50\%$  positive biopsy cores ( $p=0.001$ ).
3. PSA DT  $>12$  mo ( $p=0.001$ ).
4. Low-dose brachytherapy ( $p=0.001$ ).

In general, salvage RP should be considered only in patients with a low comorbidity, a life expectancy of at



**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 PSA, 1 wk apart, resulting in two 50% increases over the nadir.
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** Summary of treatment after hormonal therapy.

Recommendations	GR
It is recommended to stop antiandrogen therapy once PSA progression is documented.	B
Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual antiandrogen withdrawal effect is apparent.	B
No clear-cut recommendation can be made for the most effective drug for secondary hormonal manipulations because data from randomised trials are scarce.	C

GR: grade of recommendation; PSA: prostate-specific antigen.

least 10 yr, an organ-confined PCa  $\leq$  T2, Gleason score  $\leq$  7, and presurgical PSA < 10 ng/ml. Salvage RP should only be performed in experienced centres.

### Salvage cryosurgical ablation of the prostate for radiation failures

HIFU or salvage cryosurgery has been proposed as an alternative to salvage RP because both have the potential advantage of less morbidity but equal efficacy.<sup>61,62</sup> In a recent study, the 5-yr biochemical-free survival was only 50% in a cohort of men who underwent partial cryosurgical ablation of the prostate (CSAP) for radio-recurrent PCa.<sup>63</sup> In an online data registry, the outcomes of 279 patients who underwent CSAP were analysed after a median follow-up of  $21.6 \pm 24.9$  mo.<sup>64</sup> The 5-yr biochemical-free survival was 54.5%, according to the Phoenix classification. The rates of urinary incontinence and rectal fistula were 4.4%

**Table 6** Recommendations for cytotoxic therapy in castrate-resistant prostate cancer.

Recommendations	GR
Ideally, patients with CRPC should be counselled, managed, and treated with 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
Before treatment, PSA serum levels should be >2 ng/ml to ensure correct interpretation of therapeutic efficacy.	B
Potential benefits of cytotoxic therapy and expected side effects should be discussed with each individual patient.	C
In patients with metastatic CRPC who are candidates for cytotoxic therapy, docetaxel 75 mg/m <sup>2</sup> every 3 wk has shown a significant survival benefit.	A
In patients with symptomatic osseous metastases due to CRPC, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options; if not contraindicated, docetaxel should be preferred based on the significant advantage in pain relief and QoL.	A
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.	B

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

and 3.3%, respectively. Considering HIFU, available results remain questionable<sup>65</sup> even if some recent results are of interest. The largest cohort was based on 167 patients with a mean follow-up of 18 mo. No rectal complication was observed.<sup>66</sup> Based on the poor quality of the currently available data,<sup>65</sup> HIFU still cannot be recommended as a standard care procedure in patients with relapsing PCa after RT.

## Treatment of relapse after hormonal therapy

Various and different terms have been used to describe prostate cancers that relapse after initial hormonal ablation therapy, including hormone-refractory prostate cancer (HRPC), androgen-independent cancers, and hormone-independent cancers.<sup>67,68</sup> The castrate-resistant but still hormone-sensitive PCa (CRPC) has been clearly characterised, with new drugs targeting either the androgen receptor (AR) MDV3100 or androgen synthesis (abiraterone).<sup>69</sup> It is important to differentiate CRPC from true HRPC. Although CRPC responds to secondary hormonal manipulations, true HRPC resists all hormonal measures. Table 4 lists the key defining factors of CRPC. Tables 5 and 6 summarise the recommendations for the management of patients who fail hormonal therapy.

It is recommended to continue ADT with LHRH analogues, despite PSA progression, based on the data of Manni et al.<sup>70</sup> 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.<sup>71</sup> 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.

## 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.<sup>72,73</sup> Although many second-line treatment regimes have resulted in prolonged PFS, none of the approaches have resulted in an improved OS or CSS. However, second-line endocrine manipulation might be used to prolong the time until chemotherapy has to be initiated in patients with no or minimal metastatic burden and a slow PSA DT >1 yr. In patients with extensive metastatic disease, especially with predominant skeletal metastases or a rapid PSA DT <6 mo, primary chemotherapy with docetaxel should be considered.

New promising hormonal agents are under development. Both have led to the redefinition of CRPC (cells resistant to castration but still androgen sensitive) and hormone refractory status (cells definitively resistant to any hormonal manipulation), highlighting the continuing major role of the AR in these patients. The first agent, MDV3100, is a novel antiandrogen that blocks AR transfer to the nucleus, in contrast to currently available drugs where the AR remains able to transfer to the nucleus.<sup>68</sup> In a dose-finding study in 140 patients with progressive metastatic CRPC, a PSA decline >50% was seen in 56% of patients. Responses in soft-tissue metastases and stabilised bone disease were observed in 22% and 56%, respectively. The results of phase 3 clinical trials are awaited.

The second agent is the CYP17 inhibitor abiraterone acetate. In CRPC patients, this drug is able to decrease the PSA level >50% in 85% of chemotherapy-naïve patients,<sup>74</sup> in 36% after docetaxel,<sup>69</sup> and even in 26% after ketoconazole.<sup>69</sup>

A partial response, according to Response Evaluation Criteria in Solid Tumours, was seen in 18% of patients. The median time to progression was about 169 d.<sup>70</sup> The results of the clinical phase 3 trials are awaited. These agents are still in clinical trials, have not been licensed, and are therefore not yet available.

## Nonhormonal therapy (cytotoxic agents)

Based on prospective randomised phase 3 trials, docetaxel at 75 mg/m<sup>2</sup> 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 when compared with mitoxantrone.<sup>75,76</sup> The beneficial effect of docetaxel is independent of age, pain, or performance status at initiation and the presence of symptomatic or asymptomatic metastatic disease.<sup>77</sup> The most appropriate indication for chemotherapy is the clinical scenario of symptomatic metastases. In asymptomatic patients, timing of treatment is not so clear and must be discussed individually. In patients with high PSA serum levels or a rapid PSA DT <6 mo, chemotherapy should be initiated early. Early start of chemotherapy in metastatic CRPC patients results in significant survival improvement as opposed to patients with delayed initiation of systemic cytotoxic treatment. Currently, the only role for chemotherapy in nonmetastatic CRPC patients is in clinical trials, and patients should be advised to participate.<sup>77</sup>

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 OS: 25.7, 18.7, and 12.8 mo, respectively.<sup>78</sup>

Because all patients who receive docetaxel-based chemotherapy for CRPC progress within 6–8 mo, many clinical trials have investigated the role of salvage chemotherapy. The results suggest that one of the potential approaches is docetaxel rechallenge in previously responding patients as shown in retrospective trials.<sup>79–82</sup> In all other situations, vinorelbine, mitoxantrone, or molecular-targeted therapy might be considered.<sup>83</sup> Second-line satraplatin<sup>84</sup> chemotherapy recently failed to show any significant survival improvement in a large randomised trial and was rejected by the US Food and Drug Administration (FDA) and the European Medicine Evaluation Association.

Positive results were recently presented from a prospective randomised phase 3 trial comparing the therapeutic efficacy of the taxane derivate cabazitaxel combined with prednisone versus mitoxantrone combined with prednisone in 755 patients with CRPC who had progressed after or during docetaxel-based chemotherapy.<sup>85</sup> Patients in the cabazitaxel arm experienced a significantly increased OS (15.1 mo versus 12.7 mo;  $p<0.0001$ ) and an improvement in PFS (2.8 mo versus 1.4 mo;  $p<0.0001$ ). Treatment-associated World Health Organisation grade 3–4 side effects developed significantly more often in the cabazitaxel arm,

particularly haematologic (68.2% versus 47.3%;  $p < 0.0002$ ) and nonhaematologic toxicities (57.4% versus 39.8%;  $p < 0.0002$ ), respectively.

Finally, the Sipuleucel-T vaccine has been FDA approved for CRPC, based on a large phase 3 trial on 512 patients, with a 4.1-mo OS benefit but no disease progression difference between the vaccine and the placebo arms, representing the first available positive result of vaccines in.

### Palliative therapeutic option

Many patients with CRPC have painful bone metastases and are not amenable to chemotherapy, making effective palliative treatment options necessary. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses, and social workers.<sup>76</sup>

Critical issues of palliation must be addressed while considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue, and depression (i.e., palliative EBRT, cortisone, analgesics, and antiemetics).

Common complications due to skeletal metastases include bone pain, vertebral collapse, or deformity pathologic fractures and spinal cord compression. The use of zoledronate demonstrated a clinically significant effect in terms of prevention of skeletal complications and pain reduction, or even total relief of pain, in patients with CRPC.<sup>86</sup> Patients with CRPC metastatic to the bone who were given zoledronic acid 4mg every 4wk experienced a significant reduction in the number of skeletal-related events and pathologic fractures, and a significant increase in time to the first skeletal-related event.<sup>87</sup> In the most recent prospective randomised trial, the receptor activator of the nuclear factor  $\kappa$ B ligand inhibitor denosumab was compared with zoledronic acid in a cohort of about 1900 patients with CRPC and bone metastases.<sup>87,88</sup> The times to first and subsequent on-study skeletal-related events were significantly reduced by 18% in the denosumab arm. There was no statistically significant difference with regard to overall disease progression and survival. The frequency of treatment-associated side effects, especially the frequency of osteonecrosis of the jaw, was similar between both arms.

Regarding bone metastases, spinal cord compression is the most devastating complication. It must be considered an emergency, requiring immediate whole-spine magnetic resonance imaging and steroids. A surgical decompression must be systematically discussed and followed by EBRT. If, however, primary surgery is not appropriate for medical reasons, RT in combination with corticosteroids should be offered.

### Summary

The present text represents a summary, and for more detailed information and a full list of references, refer to the full-text version. These EAU guidelines (ISBN 978-90-79754-70-0) are available on the EAU Web site (<http://www.uroweb.org/guidelines/online-guidelines/>).

### Author contributions

Axel Heidenreich had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Heidenreich, Mottet. *Acquisition of data:* Heidenreich, Bellmunt, Bolla, Joniau, van der Kwast, Matveev, Mason, Schmid, Wiegel, Zattoni.

*Analysis and interpretation of data:* Heidenreich, Bellmunt, Bolla, Soniau, van der Kwast, Matveev, Mason, Schmid, Wiegel, Zattoni.

*Drafting of the manuscript:* Heidenreich, Mottet.

*Critical revision of the manuscript for important intellectual content:* Heidenreich, Bellmunt, Bolla, Joniau, van der Kwast, Matveev, Mason, Schmid, Wiegel, Zattoni.

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