European Association of Urology

Guidelines

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

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Article info

Abstract

Objective: To present a summary of the 2016 version of the European Association of Urology (EAU) – European Society for Radiotherapy & Oncology (ESTRO) – International Society of Geriatric Oncology (SIOG) Guidelines on the treatment of relapsing, metastatic, and castration-resistant prostate cancer (CRPC).

Evidence acquisition: The working panel performed a literature review of the new data (2013–2015). The guidelines were updated, and the levels of evidence and/or grades of recommendation were added based on a systematic review of the literature.

Evidence synthesis: Relapse after local therapy is defined by a rising prostate-specific antigen (PSA) level >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir after radiation therapy (RT). ^{11}C-choline positron emission tomography/computed tomography is of limited importance if PSA is <1.0 ng/ml; bone scans and computed tomography can be omitted unless PSA is >10 ng/ml. Multiparametric magnetic resonance imaging and biopsy are important to assess biochemical failure following RT. Therapy for PSA relapse after RP includes salvage RT at PSA levels <0.5 ng/ml and salvage RP, high-intensity focused ultrasound, cryosurgical ablation or salvage brachytherapy of the prostate in radiation failures. Androgen deprivation therapy (ADT) remains the basis for treatment of men with metastatic prostate cancer (PCa). However, docetaxel combined with ADT should be considered the standard of care for men with metastases at first presentation, provided they are fit enough to receive the drug. Follow-up of ADT should include analysis of PSA, testosterone levels, and screening for cardiovascular disease and metabolic syndrome. Level 1 evidence for the treatment of metastatic CRPC (mCRPC) includes, abiraterone acetate plus prednisone (AA/P), enzalutamide, radium 223 (Ra 223), docetaxel at 75 mg/m² every 3 wk and sipuleucel-T. Cabazitaxel, AA/P, enzalutamide, and radium are approved for second-line

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treatment of CRPC following docetaxel. Zoledronic acid and denosumab can be used in men with mCRPC and osseous metastases to prevent skeletal-related complications.

Conclusions: The knowledge in the field of advanced and metastatic PCa and CRPC is changing rapidly. The 2016 EAU-ESTRO-SIOG Guidelines on PCa summarise the most recent findings and advice for use in clinical practice. These PCa guidelines are the first endorsed by the European Society for Therapeutic Radiology and Oncology and the International Society of Geriatric Oncology and reflect the multidisciplinary nature of PCa management. A full version is available from the EAU office or online (http://uroweb.org/guideline/prostate-cancer/).

Patient summary: In men with a rise in their PSA levels after prior local treatment for prostate cancer only, it is important to balance overtreatment against further progression of the disease since survival and quality of life may never be affected in many of these patients. For patients diagnosed with metastatic castrate-resistant prostate cancer, several new drugs have become available which may provide a clear survival benefit but the optimal choice will have to be made on an individual basis.

1. Introduction

A prior summary of the European Association of Urology (EAU) Guidelines on prostate cancer (PCa) was published in 2013 [1]. This paper summarises the many changes that have occurred in the treatment of metastatic, relapsing, and castration-resistant PCa (CRPC) over the past 3 yr. The Guidelines on screening, diagnosis, and treatment of clinically localised and locally advanced PCa were published in a separate paper [2]. To facilitate evaluation of the quality of the information provided, levels of evidence (LEs) and grades of recommendation (GRs) have been inserted according to the general principles of evidence-based medicine [3].

2. Diagnosis and treatment of relapse after curative therapies

Physicians treating patients with prostate-specific antigen (PSA)–only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding overtreatment of patients whose disease may never affect their overall survival (OS) or quality of life (QoL). It has to be emphasised that treatment recommendations for these patients should be given after discussion with a multidisciplinary team.

2.1. Definitions

Following radical prostatectomy (RP), biochemical recurrence (BCR) is defined by two consecutive rising PSA values >0.2 ng/ml [4]. After primary radiation therapy (RT), the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology Phoenix Consensus Conference definition of PSA failure is any PSA increase ≥2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir [5]. Importantly, patients with PSA recurrence after RP or primary RT have different risks of subsequent PCa-specific mortality. For both groups, however, men with a PSA doubling time (PSA DT) of <3 mo, stage T3b or higher, Gleason score 8–10, and time to BCR of <3 yr represent a

subgroup with a high risk of developing metastases and dying from PCa [6–9].

2.2. Staging

Because biochemical recurrence (BCR) after RP or RT precedes clinical metastases by 7–8 yr on average, the diagnostic yield of common imaging techniques is poor in asymptomatic patients [10].

In men with PSA-only relapse after RP, the probability of a positive bone scan is <5% if the PSA level is <7 ng/ml [11]. Consequently, bone scan and abdominopelvic computed tomography (CT) should be considered only for patients with BCR after RP who have a high baseline PSA (>10 ng/ml) or high PSA kinetics (PSA DT <6 mo) or in patients with symptoms of bone disease [11]. Although its sensitivity is low when the PSA level is <1 ng/ml, choline positron emission tomography (PET)/CT may be helpful in selecting patients for salvage therapy after RP [12], especially if PSA DT is <6 mo [13]. Salvage RT (SRT) after RP is usually decided on the basis of BCR, without imaging.

In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18–24 mo after treatment. Given the morbidity of local salvage options, it is necessary to obtain histologic proof of the local recurrence before treating the patient [10]. Multiparametric magnetic resonance imaging (MRI) has yielded excellent results in detecting local recurrences [10,14] and can be used for biopsy targeting and guidance of local salvage treatment. Detection of local recurrence is also feasible with choline and acetate PET/CT, but PET/CT has poorer spatial resolution than MRI [15,16].

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

Early SRT provides a possibility of cure for patients with an increasing PSA after RP. More than 60% of patients who are treated before the PSA level rises to >0.5 ng/ml will achieve an undetectable PSA level [17], providing patients with an 80% chance of being progression-free 5 yr later [18]. The addition of androgen deprivation therapy (ADT) to salvage

RT has shown benefit in terms of biochemical progression-free survival (PFS) after 5 yr in retrospective series [19] and in PFS for "high-risk" tumours [20], and recent data from RTOG 9601 [21] suggested both cancer-specific survival (CSS) and OS benefits for adding 2 yr of bicalutamide to SRT. According to GETUG-AFU 16, also short-term application of a GnRH-analogue (6 mo) can significantly improve 5 yr PFS after SRT [22] (Table 1).

A large retrospective case-matching study evaluated adjuvant RT (ART) versus early SRT and included pT3N0 R0/R1 patients only (ADT was excluded); 390 of 500 patients receiving observation plus early SRT (median pre-SRT PSA was 0.2 ng/ml) were propensity matched with 390 patients receiving ART. At 2 and 5 yr after surgery, rates for no evidence of disease (NED) were 91% and 78%, respectively, for ART compared with 93% and 82%, respectively, after SRT. Subgroup analyses did not yield significant differences for the two approaches. It was concluded that early SRT does not impair PCa control but clearly helps reduce overtreatment, which is a major issue in ART [23].

2.4. Management of prostate-specific antigen relapse following radiation therapy

Salvage RP (SRP) is most likely to achieve local control. In a recent systematic review [24], SRP was shown to provide 5- and 10-yr BCR-free survival (BCR-FS) estimates ranging from 47% to 82% and from 28% to 53%, respectively. The 10-yr CSS and OS rates ranged from 70% to 83% and from 54% to 89%, respectively. SRP is associated with increased morbidity (anastomotic stricture rate 30%, rectal injury 2%) and high levels of incontinence and erectile dysfunction (ED) [25]. SRP should be considered only for patients with low comorbidity, life expectancy of at least 10 yr, a pre-SRT PSA level <10 ng/ml and biopsy Gleason score ≤7, no lymph node involvement before SRT, and initial clinical stage of T1 or T2.

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP. In a review of the use of SCAP for recurrent cancer after RT, the 5-yr biochemical disease-free survival estimates ranged from 50% to 70%. A durable response can be achieved in approximately 50% of patients with a pre-SCAP PSA level <10 ng/ml [26]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-yr BCR-FS estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15 of 46 patients (32.6%) who underwent prostate biopsy after SCAP [26]. A case-matched control study compared SRP and SCAP. The 5-yr BCR-FS rate was 61% following SRP, significantly better than the 21% rate observed after SCAP. The 5-yr OS rate was also significantly higher in the SRP group (95% vs 85%) [27]. With the use of third-generation technology, SCAP complication rates have decreased; a recent study reported an incontinence rate of 12%, retention in 7% of patients, rectourethral fistulae in 1.8%, and ED in 83% [28].

For carefully selected patients with primary localised PCa and histologically proven local recurrence, high-dose rate (HDR) or low-dose rate (LDR) brachytherapy is another salvage option with an acceptable toxicity profile [29].

Fifty-two patients were treated at the Scripps Clinic with HDR brachytherapy over a period of 9 yr [29]. With a median follow-up of 60 mo, the 5-yr biochemical control rate was 51%, and only 2% grade 3 genitourinary toxicities were reported. Comparable results came from a 42-patient phase 2 trial at Memorial Sloan Kettering Cancer Center [30]. Of note, the median pretreatment dose was 81 Gy given with intensity-modulated RT, and the prescription HDR dose of 32 Gy was delivered in four fractions over 30 h. The BCR-FS rate after 5 yr was 69% (median follow-up of 36 mo). Grade 2 late side effects were seen in 15%, and one patient developed grade 3 incontinence. These data contrast with earlier studies reporting higher rates of side effects [31].

Using LDR brachytherapy with Pd 103, long-term outcome was reported in 37 patients with a median follow-up of 86 mo [32]. The biochemical control rate after 10 yr was 54%; however, the crude rate of grade ≥2 toxicity was 46%, and grade ≥3 toxicity was 11%. These side effects were comparable with a series of 31 patients treated with salvage I 125 brachytherapy in the Netherlands. Freedom from BCR after salvage HDR and LDR brachytherapy is promising, and the rate of severe side effects at experienced centres seems to be acceptable, although numbers are small.

Salvage HIFU has also emerged as an alternative thermal ablation option for radiation-recurrent PCa. Most of the data have been generated by one high-volume centre [33]. With a median follow-up of 48 mo, 56% of men required ADT. Complication rates are comparable to other salvage treatment options, with a 0.4% rate of rectourethral fistula and a 19.5% incidence rate of grade 2/3 incontinence (Table 1).

2.5. Management of nodal relapse only

BCR rates were found to be associated with PSA at surgery and location and number of positive nodes [34]. The majority of patients treated surgically showed BCR as a consequence of micrometastatic deposits not detected with PET/CT scan. 11C-choline PET/CT has shown good sensitivity and specificity for the early detection of nodal metastases after RP [35,36]. Salvage lymph node dissection (LND) can achieve a complete biochemical response in a proportion of patients. However, most patients progress to BCR within 2 yr after surgery [35,36]. The ideal candidates for salvage LND have not been identified yet, and this approach should be reserved for highly selected patients only [35,36] (Table 1).

3. Systemic disease control (Table 1)

In patients with nonmetastatic localised PCa not suitable for curative treatment, ADT should be used only in patients requiring symptom palliation. In men with asymptomatic locally advanced T3–4 disease or BCR after attempt at cure, ADT may benefit patients with PSA >50 ng/ml and PSA DT <12 mo [37], but routine use should be avoided [38].

In symptomatic metastatic patients, immediate treatment is mandatory; however, controversy still exists

regarding asymptomatic metastatic patients because of the lack of high-quality studies. Current insights are mainly based on flawed underpowered randomised controlled trials (RCTs) with mixed patient populations (eg, locally advanced, M1a, M1b status) and a variety of ADT treatments and follow-up schedules. ADT was shown to be the most cost-effective therapy if started at the time that the patient developed symptomatic metastases [39]. A Cochrane review extracted four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the Eastern Cooperative Oncology Group (ECOG) 7887 study [40]. These studies were conducted in the pre-PSA era and included patients with advanced PCa who received early versus deferred ADT as either primary therapy or adjuvant after RP. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications.

3.1. Hormonal therapy

3.1.1. Luteinising hormone-releasing hormone: agonists and antagonists

Surgical castration is considered the gold standard for ADT. Current methods have shown that the mean testosterone level after surgical castration is 15 ng/dl [41], and testosterone levels <20 ng/dl are associated with improvement in outcomes compared with men who only reach a level of between 20 and 50 ng/dl [42,43]. Luteinising hormone-releasing hormone (LHRH) agonists have replaced surgical castration as the standard of care in hormonal therapy because these agents have potential for reversibility, avoid the physical and psychological discomfort associated with orchiectomy, and have a lower risk of cardiotoxicity than observed with diethylstilbestrol while providing similar oncologic efficacy [44]. LHRH antagonists are also available. They bind immediately and competitively to LHRH receptors, leading to a rapid decrease in luteinising hormone, follicle-stimulating hormone, and testosterone levels without the flare phenomenon seen with agonists, which may be particularly important for patients with symptomatic locally advanced or metastatic disease. In addition, an extended follow-up study has been published suggesting better progression-free survival compared with monthly leuprorelin [45]. However, definitive superiority over the LHRH agonists remains to be proven, and a lack of long-acting depot formulation makes them less practical.

3.1.2. Antiandrogens

Nonsteroidal antiandrogens (NSAAs) do not suppress testosterone secretion but are commonly used to ameliorate the clinical effects of the initial testosterone surge associated with LHRH agonists [46]. Pharmacologic side effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profile than flutamide and nilutamide [47]. All three agents share a common potential for liver toxicity (occasionally fatal), and liver enzymes must be monitored regularly. When used as monotherapy, it is claimed that libido and overall physical performance are preserved [48]. In general, bone mineral

density (BMD) is maintained with bicalutamide [48]; however, a Cochrane systematic review [49] comparing NSAA monotherapy and castration (either medical or surgical) revealed that NSAAs were considered to be less effective in terms of OS, clinical progression, and treatment failure, and treatment discontinuation due to adverse events (AEs) was more common.

Systematic reviews of antiandrogens in combination with LHRH agonists have shown that combined androgen blockade using an NSAA appears to provide a small survival advantage (<5%) versus monotherapy (surgical castration or LHRH agonists) [50–52].

3.2. Intermittent androgen deprivation therapy

Three independent reviews [53–55] and a meta-analysis [56] have evaluated the clinical efficacy of intermittent ADT (IAD). All of these reviews included eight RCTs of which only three were conducted in patients with M1 disease only. SWOG 9346 trial [57] is the largest trial conducted in M1b patients. Of 3040 selected patients, only 1535 had an adequate PSA response (<4 ng/ml) to allow randomisation (ie, only 50% of M1b patients might be candidates for IAD). In addition, the prespecified noninferiority limit was not achieved (median OS: 5.8 vs 5.1 yr; hazard ratio [HR]: 1.1; 95% confidence interval [CI], 0.99–1.23), suggesting that we cannot rule out a 20% greater risk of death with intermittent therapy than with continuous therapy. More concrete conclusions are hampered by a lack of events. Other trials did not show any survival difference with an HR for OS of 1.04 (95% CI, 0.91–1.19). These reviews and the meta-analysis came to the following conclusion: There was no difference in OS or CSS between IAD and continuous androgen deprivation. A recent review of the available phase 3 trials highlighted the limitations of most trials and suggested a cautious interpretation of the noninferiority results. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side effects such as hot flushes.

3.3. Hormonal treatment combined with chemotherapy

Three large RCTs were conducted [58–60]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/m^2 every 3 wk; within 3 mo of ADT initiation). The primary objective in all three studies was OS.

In the GETUG 15 trial [58], all patients had newly diagnosed M1 PCa, either primary or after a primary treatment. They were stratified based on prior local treatment and Glass risk factors [59]. In the CHAARTED trial [60], the same inclusion criteria applied, although patients were stratified according to disease volume; high volume was defined as either presence of visceral metastases or four or more bone metastases, with at least one outside the spine and pelvis. The third study, STAMPEDE [61], was a multiarm, multistage trial in which the reference arm (standard of care, mostly ADT) included 1184 patients. One of the experimental arms was ADT combined with

Table 1 – Guidelines for imaging and second-line therapy after treatment with curative intent

Local salvage treatment	LE	GR
BCR after RP		
Offer patients with a PSA rise from the undetectable range and favourable prognostic factors (pT3a or lower, time to BCR >3 yr, PSA DT >12 mo, Gleason score ≤7) surveillance and possibly delayed salvage radiotherapy.	3	B
Treat patients with a PSA rise from the undetectable range with salvage RT. The total dose of salvage RT should be at least 66 Gy and should be given early (PSA <0.5 ng/ml).	2	A
BCR after RT		
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage RP.	3	B
Due to the increased rate of side effects, perform salvage RP in experienced centres.	3	A
Offer or discuss high-intensity focused ultrasound, cryosurgical ablation, and salvage brachytherapy with patients without evidence of metastasis and with histologically proven local recurrence. Inform patients about the experimental nature of these approaches.	3	B
Systemic salvage treatment		
Do not routinely offer ADT to asymptomatic men with BCR.	3	A
Do not offer ADT to patients with a PSA DT >12 mo.	3	B
If salvage ADT (after primary RT) is started, offer intermittent therapy to responding patients.	1b	A

ADT = androgen-deprivation therapy; BCR = biochemical recurrence; GR = grade of recommendation; LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen; PSA DT = prostate-specific antigen doubling time; RP = radical prostatectomy; RT = radiotherapy.

Table 2 – Key findings: hormonal treatment combined with chemotherapy in men presenting with metastatic disease

Study	Population	Patients, n	Median FU, mo	Median OS, mo		HR	p value
				ADT + D	ADT		
Gravis et al [58]	M1	385	50	58.9	54.2	1.01 (0.75–1.36)	0.955
Gravis et al [59]	HV *: 47%		82.9	60.9	46.5	0.9 (0.7–1.2)	0.44
Sweeney et al [60]	M1 HV *: 65%	790	28.9	57.6	44	0.61 (0.47–0.8)	<0.001
STAMPEDE [61]	M1 (61%), N+ (15%), relapse	1184					
		593 D	43	81	71	0.78 (0.66–0.93)	0.006
		593 D + ZA		76	NR	0.82 (0.69–0.97)	0.022
	M1 only	725 + 362 D		60	45	0.76 (0.62–0.92)	0.005

ADT = androgen deprivation therapy; D = docetaxel; FU = follow-up; HR = hazard ratio; HV = high volume; NR = not reported; ZA = zoledronic acid.
* HV indicates either visceral metastases or more than four bone metastases with at least one outside the spine and pelvis.

docetaxel (n = 593), and another was ADT combined with docetaxel and zoledronic acid (n = 593). Patients were included with either M1 or N1 or had at least two of the following adverse criteria: T3/4, PSA ≥40 ng/ml, or Gleason 8–10. In addition, relapsed patients after local treatment were included if they had one of the following criteria: PSA ≥4 ng/ml with PSA DT <6 mo, PSA ≥20 ng/ml, N1, or M1. No stratification was used regarding metastatic disease volume. The key findings are summarised in Table 2.

In the three trials, toxicity was mainly haematologic with approximately 12–15% grade 3–4 neutropenia and 6–12% grade 3–4 febrile neutropenia. Concomitant use of granulocyte colony-stimulating factor receptor was shown to be helpful, and its use should be based on available guidelines [62]. Based on these data, docetaxel combined with ADT should be considered as a new standard for men presenting with metastases at first presentation, provided they are fit enough to receive the drug (Table 3).

3.4. Follow-up during hormonal treatment

The main objectives of follow-up in men on ADT are to ensure treatment compliance, to monitor treatment response and side effects, and to identify the development of CRPC. Clinical follow-up is mandatory on a regular basis and cannot be replaced by laboratory tests or imaging modalities. It is of the utmost importance in metastatic situations to advise patients about early signs of spinal cord compression and to check for occult cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction), or bone lesions that pose an increased fracture risk. Treatment response may be assessed using the change in serum PSA level as a surrogate end point for survival [63]. Asymptomatic patients with a stable PSA level do not require further imaging. Table 4 summarises the guidelines for follow-up during hormonal therapy. New-onset bone pain requires a bone scan, as does PSA progression suggesting CRPC status, if a treatment modification is considered. The Prostate Cancer Clinical Trials Working Group (PCWG2) clarified the definition of bone scan progression, at least for patients enrolled in clinical trials, as the appearance of at least two new lesions [64] that are later confirmed. Suspicion of disease progression indicates the need for additional imaging modalities guided by symptoms or possible subsequent treatments.

The measurement of serum testosterone levels should also be considered part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. A 3- to 6-mo assessment of the testosterone level might be performed to evaluate the effectiveness of treatment and to ensure that 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

Table 3 – Guidelines for hormonal treatment of metastatic prostate cancer

Recommendation		LE	GR
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.		1a	A
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk of potentially catastrophic sequelae of advanced disease (spinal cord compression, pathologic fractures, ureteral obstruction, extraskeletal metastasis).		1b	A
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.		1b	A
In M1 asymptomatic patients, discuss deferred castration with well-informed patients because it lowers the treatment side effects, provided the patient is closely monitored.		2b	B
Anti-androgens			
Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.		2	B
In M1 patients treated with an LHRH agonist, offer short-term administration of antiandrogens to reduce the risk of the "flare-up" phenomenon.		2a	A
Start antiandrogens used for flare-up prevention on the same day that an LHRH analogue is started or for up to 7 d before the first LHRH analogue injection if patient has symptoms. Treat for 4 wk.		3	A
Do not offer antiandrogen monotherapy in M1 patients.		1a	A
Intermittent treatment			
Population	In asymptomatic M1 patients, offer intermittent treatment to highly motivated men with a major PSA response after the induction period.	1b	B
Threshold to start and stop ADT	• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. Stop treatment when the PSA level is <4 ng/ml after 6–7 mo of treatment. • Resume treatment when the PSA level is >10–20 ng/ml (or to the initial level if <20 ng/ml).	1b	B
Drugs	In M1 patients, offer combined treatment with LHRH agonists and NSAA.	1b	A

ADT = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence; LHRH = luteinising hormone-releasing hormone; NSAA = nonsteroidal antiandrogen; PSA = prostate-specific antigen.

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

During long-term therapy, ADT reduces bone mineral density (BMD) and increases the risk of fractures [65]. In the absence of associated risk factors, it is recommended that BMD and serum vitamin D and calcium levels should be measured every 2 yr [66]. Treatment should be individualised; however, for men with a BMD T-score lower than −2.5 and one risk factor or more or with hip and vertebral fractures, use of bisphosphonates should be discussed. Specialists should also screen patients for the development of metabolic sequelae associated with ADT such as alterations in lipid profiles and decreased insulin sensitivity [67]. Although little is known about the optimal strategy to mitigate the adverse metabolic effects, the Guidelines Panel recommends treatment strategies to reduce the risk of diabetes and cardiovascular disease [68]. Patients should be given advice on modifying their lifestyle (eg, diet, exercise, smoking cessation) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension. Furthermore, the risk–benefit ratio of ADT must be considered for patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

4. Castration-resistant prostate cancer (Table 4)

4.1. Definition

CRPC is defined as castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression:

• Biochemical progression: Three consecutive rises in PSA 1 wk apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml
• Radiologic progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a

Table 4 – Guidelines for follow-up during hormonal treatment

Recommendation	GR
Evaluate patients at 3–6 mo after the initiation of treatment.	A
As a minimum, tests should include serum PSA measurement, physical examination, serum testosterone, and careful evaluation of symptoms to assess the treatment response and side effects.	A
In patients undergoing intermittent androgen deprivation, monitor PSA and testosterone at fixed intervals during the treatment pause (at 3-mo intervals).	A
In patients with stage M1 disease with good treatment response, schedule follow-up every 3–6 mo. As a minimum requirement, include a disease-specific history, physical examination, serum PSA, haemoglobin, and serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year.	A
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	A
When disease progression occurs or if the patient does not respond to treatment, adapt/individualise follow-up.	A
In patients with suspected progression, assess the testosterone level. By definition, CRPC requires a testosterone level <50 ng/ml (<1.7 nmol/l).	B
Do not offer routine imaging to otherwise stable patients.	B

CRPC = castration-resistant prostate cancer; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen.

Table 5 – Guidelines for management of castration-resistant prostate cancer

Recommendation	LE	GR
Ensure that testosterone levels are confirmed to be <50 ng/ml before diagnosing CRPC.	4	A
Do not treat patients for nonmetastatic CRPC outside of a clinical trial.	3	A
Counsel, manage, and treat patients with mCRPC in a multidisciplinary team.	3	A
In men treated with maximal androgen blockade, stop antiandrogen therapy once PSA progression is documented. *Comment: At 4–6 wk after discontinuation of flutamide or bicalutamide, an eventual antiandrogen withdrawal effect will be apparent.*	2a	A
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, and extent of disease (alphabetical order: abiraterone, cabazitaxel docetaxel, enzalutamide, Ra 223, sipuleucel-T).	1b	A
Offer patients with mCRPC who are candidates for cytotoxic therapy, docetaxel with 75 mg/m^2 every 3 wk.	1a	A
Base second-line treatment decisions of mCRPC on pretreatment performance status, comorbidities, and extent of disease.		B
Offer bone-protective agents to patients with skeletal metastases to prevent osseous complications; however, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	1a	B
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	1b	A
Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, radionuclides, and adequate use of analgesics.	1a	B
In patients with spinal cord compression, start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	1b	A

CRPC = castration-resistant prostate cancer; GR = grade of recommendation; LE = level of evidence; mCRPC = metastatic castration-resistant prostate cancer.

soft tissue lesion using the Response Evaluation Criteria in Solid Tumours [8,25]

Symptomatic progression alone must be questioned and subject to further investigation; it is not sufficient for diagnosing CRPC.

Post-treatment PSA surveillance has resulted in earlier detection of progression. Although approximately one-third of men with rising PSA will develop bone metastases within 2 yr [69], no available studies suggest a benefit for immediate treatment. In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity, and PSA DT have been associated with time to first bone metastasis, bone metastasis-free survival, and OS [69,70]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group [71] suggested that a bone scan be performed when PSA reached 2 ng/ml and that if this was negative, it should be repeated when PSA reached 5 ng/ml and again after every doubling of the PSA based on PSA testing every 3 mo for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level (Table 5).

Two trials have shown a marginal survival benefit for patients with metastatic CRPC (mCRPC) remaining on LHRH analogues during second- and third-line therapies [72,73]. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression; therefore, it should be continued indefinitely in these patients.

4.2. First-line treatment in metastatic castration-resistant prostate cancer

Abiraterone was evaluated in 1088 chemonaïve mCRPC patients in the phase 3 trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [74]. The main stratification factors were ECOG performance status 0 or 1 and asymptomatic or mildly symptomatic disease. OS and radiographic PFS (rPFS)

were the co–primary end points. After a median follow-up of 22.2 mo, there was significant improvement of rPFS (median: 16.5 vs 8.2 mo; HR: 0.52; $p < 0.001$), and the trial was unblinded. At the final analysis, with a median follow-up of 49.2 mo, the OS end point was significantly positive (34.7 vs 30.3 mo; HR: 0.81; 95% CI, 0.70–0.93; $p = 0.0033$) [75]. AEs related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone but were mostly grades 1–2.

A randomised phase 3 trial (PREVAIL) [76] included a similar patient population and compared enzalutamide and placebo. Men with visceral metastases were accepted, although the numbers were small. Corticosteroids were allowed but were not mandatory. PREVAIL was conducted in a chemonaïve mCRPC population of 1717 men and showed significant improvement in both co–primary end points of rPFS (HR: 0.186; 95% CI, 0.15–0.23; $p < 0.0001$) and OS (HR: 0.706; 95% CI, 0.6–0.84; $p < 0.001$). The most common clinically relevant AEs were fatigue and hypertension.

In 2010, a phase 3 trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [77]. After a median follow-up of 34 mo, median survival was 25.8 mo in the sipuleucel-T group compared with 21.7 mo in the placebo group, leading to a significant HR of 0.78 ($p = 0.03$). No PSA decline was observed, and PFS was equivalent in both arms. Overall tolerance was very good, with more cytokine-related grade 1–2 AEs in the sipuleucel-T group but the same amount of grade 3–4 AEs in both arms. Sipuleucel-T is not available in Europe.

A significant improvement in median survival of 2.0–2.9 mo occurred with docetaxel-based chemotherapy compared with mitoxantrone plus prednisone therapy [78]. The standard first-line chemotherapy is docetaxel 75 mg/m^2 in three weekly doses combined with prednisone 5 mg twice a day up to 10 cycles. Prednisone can be omitted if there are contraindications or no major symptoms. Several poor prognostic factors have been described before docetaxel treatment: PSA >114 ng/ml, PSA DT <55 d, or the presence of visceral metastases [79]. A better risk group definition

was presented more recently based on the TAX 327 study cohort: The independent prognostic factors were visceral metastases, pain, anaemia (haemoglobin <13 g/dl), bone scan progression, and prior estramustine.

Patients were categorised into three risk groups of low risk (no or one factor), intermediate (two factors), and high risk (three or four factors) and showed three significantly different median OS estimates of 25.7, 18.7, and 12.8 mo, respectively [80]. Age by itself is not a contraindication to docetaxel, but attention must be paid to closer monitoring and comorbidities [81]. In men with mCRPC who are thought to be unable to tolerate the standard regimen, using docetaxel 50 mg/m^2 every 2 wk might be considered. It was well tolerated with fewer grade 3–4 AEs and prolonged time to treatment failure [82].

The only bone-targeted drug associated with a survival benefit is Ra 223, an alpha emitter. In a large phase 3 trial (ALSYMPCA), 921 patients with symptomatic mCRPC who failed or were unfit for docetaxel were randomised to six injections, with one injection administered every 4 wk, of 50 kBq/kg Ra 223 or placebo, plus standard of care. The primary end point was OS. Ra 223 significantly improved median OS by 3.6 mo (HR: 0.70; $p < 0.001$) [83]. It was also associated with prolonged time to first skeletal event and improvement in pain scores and QoL. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with Ra 223, did not differ significantly from that in the placebo arm [83]. Ra 223 was effective and safe regardless of whether or not the patients were pretreated with docetaxel [84].

Treatment decisions will need to be individualised, and a summary of the issues regarding sequencing were discussed in a paper produced following the St Gallen Consensus Conference [85]. Baseline examinations should include history and clinical examination as well as baseline blood tests (PSA, full blood count, renal function, liver function, alkaline phosphatase), bone scan, and CT of chest abdomen and pelvis [85]. PSA alone is not reliable enough for monitoring disease activity in advanced CRPC because visceral metastases may develop in men without rising PSA [86]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements, and clinical benefit in assessing men with CRPC [64]. A majority of experts suggested regular review and repeated blood profile every 2–3 mo, with bone scintigraphy and CT scans at least every 6 mo, even in the absence of a clinical indication [85]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost, and patients with no objective benefit should have treatment modified. This panel stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of three criteria (PSA progression, radiographic progression, and clinical deterioration) should be fulfilled to stop treatment.

4.3. Second-line treatment options and beyond in metastatic castration-resistant prostate cancer

The second-line options available will be affected by the treatment chosen as first-line treatment for CRPC.

Generally, because of concerns about cross-resistance between hormone-manipulating agents [87], if either abiraterone or enzalutamide were used as first-line treatment and the patient remains clinically suitable, docetaxel would be offered next. In men who responded to first-line docetaxel, retreatment is associated with a PSA response in approximately 60% with a median time to progression of approximately 6 mo, whereas treatment-associated toxicity was minimal and similar to that of first-line docetaxel [88,89]. No survival improvement has been demonstrated with docetaxel rechallenge in responders.

Cabazitaxel is a taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective randomised phase 3 trial (TROPIC trial) comparing cabazitaxel plus prednisone versus mitoxantrone plus prednisone in 755 patients with mCRPC who had progressed after or during docetaxel-based chemotherapy [90]. Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/d), respectively. OS was the primary end point, which was significantly longer with cabazitaxel (median: 15.1 vs 12.7 mo; $p < 0.0001$). Treatment-associated World Health Organisation grade 3–4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological toxicity (68.2% vs 47.3%; $p < 0.0002$) but also nonhaematological toxicity (57.4% vs 39.8%; $p < 0.0002$). This drug should be administered preferably with prophylactic granulocyte colony-stimulating factor and by physicians with expertise in handling neutropenia and sepsis [91].

Positive preliminary results of the large phase 3 COU-AA-301 trial were reported after a median follow-up of 12.8 mo [92], and the final results have been reported more recently [93]. A total of 1195 patients with mCRPC were randomised 2:1 to abiraterone acetate plus prednisone or placebo plus prednisone. All patients had progressive disease based on the PCWG2 criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 mo, median survival in the abiraterone group was 15.8 mo compared with 11.2 mo in the placebo arm (HR: 0.74; $p < 0.0001$). The benefit was observed in all subgroups, and all secondary objectives were in favour of abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3–4 side effects did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly grades 1–2 (fluid retention, oedema, and hypokalaemia).

The planned preliminary analysis of the AFFIRM study was published in 2012 [94]. This trial randomised 1199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory but could be prescribed and were received by 30% of the population. The primary end point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 mo, median survival in the enzalutamide group was 18.4 mo compared

with 13.6 mo in the placebo arm (HR: 0.63; $p < 0.001$). This led to the recommendation that the study be halted and unblinded. The benefit was observed regardless of age, baseline pain intensity, and type of progression. All secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm. There was 0.6% incidence of seizures in the enzalutamide group compared with none in the placebo arm.

4.4. Bone-targeting agents

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [95], even as a single fraction [96]. Apart from Ra 223, however, no bone-targeted drug has been associated with improved survival.

Zoledronic acid has been used in mCRPC to reduce skeletal-related events (SREs). This study was conducted when no active anticancer treatments but docetaxel were available. In total, 643 patients who had CRPC [97] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg, every 3 wk for 15 consecutive months or placebo. The 8-mg dose was poorly tolerated and was reduced to 4 mg but did not show a significant benefit. However, at 15 and 24 mo of follow-up, patients treated with 4 mg zoledronic acid had fewer SREs compared with the placebo group (44% vs 33%; $p = 0.021$) and, in particular, had fewer pathologic fractures (13.1% vs 22.1%; $p = 0.015$). Furthermore, the time to first SRE was longer in the zoledronic acid group.

The toxicity (eg, jaw necrosis) of these drugs must always be kept in mind. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery, or dental infection, as well as by long-term intravenous bisphosphonate administration [98].

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone metastasis–free survival compared with placebo (median benefit: 4.2 mo; HR: 0.85; $p = 0.028$) [99]. This benefit did not translate into a survival difference (43.9 vs 44.8 mo, respectively), and neither the US Food and Drug Administration nor the European Medicines Agency approved denosumab for this indication.

The efficacy and safety of denosumab ($n = 950$) compared with zoledronic acid ($n = 951$) in patients with mCRPC was assessed in a phase 3 trial [100]. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathologic fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 versus 17.1 mo, respectively (HR: 0.82; $p = 0.008$). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm ($p < 0.0001$). In a recent post hoc reevaluation of end points, denosumab showed identical results when comparing SREs and symptomatic skeletal events [99].

4.5. Palliative therapeutic options

CRPC is usually a debilitating disease, often affecting elderly men. A multidisciplinary approach is often required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists, and social workers [101]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue, and depression, which often occur.

5. Conclusions

The present text represents a summary of the EAU-ESTRO-SIOG. For more detailed information and a full list of references, refer to the full-text version. These guidelines are available on the EAU Web site (http://uroweb.org/guideline/prostate-cancer/).

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