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Review – Prostate Cancer

EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer

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Abstract

Objective: To present a summary of the 2020 version of the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy & Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-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 (2016–2019). 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: Prostate-specific membrane antigen positron emission tomography computed tomography scanning has developed an increasingly important role in men with biochemical recurrence after local therapy. Early salvage radiotherapy after radical

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prostatectomy appears as effective as adjuvant radiotherapy and, in a subset of patients, should be combined with androgen deprivation. New treatments have become available for men with metastatic hormone-sensitive prostate cancer (PCa), nonmetastatic CRPC, and metastatic CRPC, along with a role for local radiotherapy in men with low-volume metastatic hormone-sensitive PCa. Also included is information on quality of life outcomes in men with PCa.

Conclusions: The knowledge in the field of advanced and metastatic PCa and CRPC is changing rapidly. The 2020 EAU-EANM-ESTRO-ESUR-SIOG guidelines on PCa summarise the most recent findings and advice for use in clinical practice. These PCa guidelines are first endorsed by the EANM 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: This article summarises the guidelines for the treatment of relapsing, metastatic, and castration-resistant prostate cancer. These guidelines are evidence based and guide the clinician in the discussion with the patient on the treatment decisions to be taken. These guidelines are updated every year; this summary spans the 2017–2020 period of new evidence.

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1. Introduction

A prior summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2017 [1]. This paper summarises the many changes that have occurred in the treatment of relapsing, metastatic, and castration-resistant PCa (CRPC) over the past 4 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, a grade form has been completed for each recommendation also providing the strength of recommendation based on a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) process [3].

2. Diagnosis and treatment of relapse after curative therapies

Between 27% and 53% of all patients undergoing radical prostatectomy (RP) or radiation therapy (RT) develop a rising prostate-specific antigen (PSA) level (PSA recurrence). Physicians face a difficult set of decisions in attempting to delay the onset of metastatic disease and death whilst avoiding overtreatment of patients whose disease may never affect their overall survival (OS) or quality of life (QoL).

2.1. Definitions

Following RP, the threshold that best predicts further metastases is a PSA level of >0.4 ng/mL and rising [4]. However, with access to ultrasensitive PSA testing, a rising PSA level much below this level will be a cause for concern. After primary RT with or without short-term hormonal manipulation, the Radiation Therapy Oncology Group (RTOG) and the American Society for Radiation Oncology Phoenix Consensus Conference definition of PSA failure (with an accuracy of $>80\%$ for clinical failure) is any

PSA increase of ≥ 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. A recent systematic review and meta-analysis investigated the impact of biochemical recurrence (BCR) on hard end points and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, and PCa-specific and overall mortality [6]. However, the effect size of BCR as a risk factor for mortality is highly variable, suggesting that only certain patient subgroups with BCR might be at an increased risk of mortality.

The risk of subsequent metastases, and PCa-specific and overall mortality may be predicted by the initial clinical and pathological factors (eg, T category, PSA, International Society of Urological Pathology [ISUP] grade) and PSA kinetics (PSA doubling time [PSA-DT] and interval to PSA failure) [6]. Based on the meta-analysis, the panel suggested a new stratification, emphasising that the patient group experiencing BCR is a heterogeneous group. This stratification made a distinction between patients with EAU low-risk BCR (for RP: PSA-DT >1 yr and pathological ISUP grade <4 ; for RT: interval to biochemical failure >18 mo and biopsy ISUP grade <4) and EAU high-risk BCR (for RP: PSA-DT <1 yr or pathological ISUP grade 4–5; for RT: interval to biochemical failure <18 mo or biopsy ISUP grade 4–5), since not all patients with BCR will have similar outcomes. The stratification into “EAU low-risk” or “EAU high-risk” BCR group has recently been validated in a separate European cohort, suggesting that low-risk patients may not require immediate intervention [7].

2.2. Staging

BCR after RP or RT precedes clinical metastases by 7–8 yr on average; the diagnostic yield of common imaging techniques (bone scans, computed tomography [CT], and magnetic resonance imaging [MRI] scans) are poor in asymptomatic patients with low PSA [8].

In men with PSA-only relapse after RP, salvage RT (SRT) has often been initiated on the basis of BCR, without imaging. In patients with BCR after RP, the sensitivity of choline positron emission tomography (PET) is strongly influenced by PSA level and kinetics [9], and drops to suboptimal values in patients with a low PSA level (only 5–24% when the PSA level is <1 ng/mL) [10]; after RP, a possible PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL [10]. However, prostate-specific membrane antigen (PSMA) PET/CT has been shown to be substantially more sensitive than other imaging modalities, especially for PSA levels <1 ng/mL [11,12]. (Scan positivity rates of ^{68}Ga -PSMA PET scans for PSA levels <1 ng/mL are 33% [95% confidence interval {CI}: 16–51], 45% [95% CI: 39–52], and 59% [95% CI: 50–68] for PSA categories 0–0.19, 0.2–0.49, and 0.5–0.99 ng/mL, respectively [13].) Indeed, ^{68}Ga -PSMA PET/CT identified the site of recurrence in 59 of 88 patients (67%) in a prospective trial [14].

In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided that the biopsies are obtained 18–24 mo after treatment. Given the morbidity of local salvage options, it is necessary to obtain histological proof of the local recurrence before treating the patient [8]. Multiparametric MRI has yielded excellent results in detecting local recurrences [8,15], and can be used for biopsy targeting and guidance of local salvage treatment. Detection of local recurrence is also feasible with choline and PSMA PET/CT, but PET/CT has poorer spatial resolution than MRI [16,17]. Although it is clear that men with a rising PSA level after RT but not meeting the Phoenix criteria may have detectable recurrence on PSMA PET scans [18].

2.3. Management of PSA relapse following RP

Early SRT provides a possibility of cure for patients with an increasing PSA level after RP. Previously, men were offered treatment without imaging because of low sensitivity. However, increasing use of PSMA PET suggests that it may stratify men into groups with high response (negative findings or recurrence confined to the prostate) and poor response (positive nodes or distant disease) to SRT [19]. In men with a negative PSMA PET/CT scan who received SRT, 85% (23 out of 27) demonstrated a treatment response, compared with a further PSA increase in 65% of those not treated (22 out of 34). In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (29 out of 36) responded to SRT. Currently, no data exist on the impact on final outcome, and there is great debate about what to do with men identified as oligometastatic on PSMA PET who would not be detected on conventional imaging.

The optimal SRT dose has not been well defined; however, it should be at least 66 Gy to the prostatic fossa (plus/minus the base of the seminal vesicles, depending on the pathological stage after RP) [20,21]. More than 60% of patients who are treated before the PSA level rises to >0.5 ng/mL will achieve an undetectable PSA level [20], providing patients with an 80% chance of being progression free 5 yr later [22]. The RAVES and RADICAL trials assessing SRT in post-RP patients with PSA levels exceeding 0.1–

0.2 ng/mL showed 5-yr freedom from BCR and BCR-free survival rates of 88% [23,24]. SRT has been shown to provide a survival benefit mainly in patients with a short PSA-DT [25] (<6 mo).

In retrospective data, the addition of androgen deprivation therapy (ADT) to SRT has shown a benefit in terms of biochemical progression-free survival (PFS) after 5 yr [26] and in PFS for “high-risk” tumours [27]. Recent data from RTOG 9601 suggested improvement in both cancer-specific survival (CSS) and OS by adding 2 yr of bicalutamide to SRT [28]. GETUG-AFU 16 confirmed that short-term application of a gonadotropin-releasing hormone analogue (6 mo) can significantly improve 10 yr PFS and metastasis-free survival after SRT [29]. A recent review addressing the benefit from combining ADT with SRT suggested risk stratification of patients based on the pre-SRT PSA (<0.5, 0.6–1.0, and >1 ng/mL), margin status, and ISUP grade, as a framework to individualise treatment [30]. In a retrospective multicentre study including 525 patients, only in patients with more aggressive disease characteristics (pT3b/4 and ISUP grade >4, or pT3b/4 and a PSA level at early SRT of >0.4 ng/mL), the administration of concomitant ADT was associated with a reduction in distant metastasis [31]. Similarly, in a retrospective analysis of 1125 patients, stage \geq pT3b, Gleason score \geq 8, and a PSA level at SRT of >5 ng/mL were identified as risk factors for clinical recurrence. A significant effect of long-term ADT was observed in patients with two or more adverse features. For patients with a single risk factor, short-term ADT was sufficient, whilst patients without risk factors showed no significant benefit from concomitant ADT [32].

2.4. Management of PSA relapse following RT

Local salvage treatment should be considered only for selected patients with low comorbidity, life expectancy of at least 10 yr, a presalvage therapy PSA level of <10 ng/mL, initial ISUP \leq 3 initial clinical stage of T1 or T2, and no lymph node involvement. Salvage RP (SRP) is most likely to achieve local control. In a systematic review, Chade et al [33] showed that SRP provided 5- and 10-yr BCR-free survival 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 in inexperienced hands (anastomotic stricture rate up to 30% and rectal injury up to 2%) and high levels of incontinence and erectile dysfunction (ED) [34].

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP. In a review, 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 of <10 ng/mL [35]. However, positive biopsies were observed in 15 of 46 patients (32.6%) who underwent prostate biopsy after SCAP [35]. A case-matched control study compared SRP and SCAP; the 5-yr OS rate was significantly higher in the SRP group (95% vs 85%) [36]. With the use of third-generation technology, SCAP complication

rates have decreased but remain similar to SRP: an incontinence rate of 12%, retention in 7% of patients, rectourethral fistulae in 1.8%, and ED in 83% [37]. Salvage high-intensity focused ultrasound has also emerged as an alternative thermal ablation option for radiation-recurrent PCa [38].

For carefully selected patients, high-dose rate (HDR) or low-dose rate (LDR) brachytherapy is another salvage option with an acceptable toxicity profile in highly selected cases [39]. Fifty-two patients were treated with HDR brachytherapy over a period of 9 yr [39]. 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 [40]. The actuarial BCR-free survival rate using the Phoenix criteria 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. Using LDR brachytherapy with palladium (Pd)-103, long-term outcome was reported in 37 patients with a median follow-up of 86 mo [41]. The biochemical control rate (Phoenix criteria) after 10 yr was 54%; however, the crude rate of grade ≥ 2 toxicity was 46% and that of grade ≥ 3 toxicity was 11%. A multicentre prospective study with 92 evaluable patients and a median follow-up of 54 mo demonstrates 14% rate of grade 3 late toxicity and no grade 4/5 toxicity. Outcomes will be available when all patients have a minimum of 5 yr of follow-up [42]. In general, there is a lack of quality data, which prohibits any recommendation regarding the indications for specific salvage treatments.

2.5. Management of pelvic nodal relapse only

Novel imaging modalities improve the early detection of nodal metastases [43]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [43–45]. The majority of treated patients showed BCR, but clinical recurrence-free survival and 10-yr CSS of over 70% have been reported [44,46]. Neither the template nor the real value of nodal salvage dissection is available. It must, however, be

remembered that the imaging modalities underevaluate the real nodal involvement. BCR rates were found to be dependent on PSA at surgery and on the location and number of positive nodes [47]. Addition of RT to the lymphatic template after salvage lymph node dissection may improve the BCR rate [48]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival (Table 1) [49].

3. Metastatic PCa

The definition of metastatic spread has relied upon the detection of lesions on CT scan and bone scan. This has also been the basis of the available prospective data. The influence on treatment and outcome of newer and more sensitive imaging has not been assessed yet.

Median survival of treated patients with newly diagnosed metastases is approximately 42 mo with ADT monotherapy [50]; however, the M1 population is heterogeneous. Several prognostic factors for survival have been suggested, including the number and location of bone metastases, presence of visceral metastases, ISUP grade, performance status (PS), initial PSA, and alkaline phosphatase (ALP), but only few have been validated [51–64]. “Volume” of disease as a potential predictor was introduced by Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) [54–56] and also in LATITUDE [57]. Having low-volume/low-burden metastatic disease, by the CHAARTED criteria, has been shown to be predictive of the benefit of addition of prostate RT [58] in a powered subgroup analysis, with a OS benefit of this additional local treatment only in the patients with low-volume disease (Table 2).

3.1. Hormonal therapy

Primary ADT has been the standard of care for over 50 yr [59]. A recently updated Cochrane review suggests a benefit for early versus referred ADT [60]. Surgical castration is considered the gold standard for ADT. Current methods

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

Local salvage treatment	Strength rating
<i>Recommendations for biochemical recurrence after radical prostatectomy</i>	
Offer PSA monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
Offer SRT to patients with a PSA rise from the undetectable range. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
Offer androgen deprivation therapy in addition to SRT to men with biochemical recurrence.	Weak
<i>Recommendations for biochemical recurrence after radiotherapy</i>	
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage RP.	Weak
Salvage RP should be performed only in experienced centres.	Weak
Offer salvage HIFU, salvage cryosurgical ablation, and salvage brachytherapy only to patients with proven local recurrence within a clinical trial setting or well-designed prospective cohort study.	Strong
<i>Recommendations for systemic salvage treatment</i>	
Do not offer ADT to M0 patients with a PSA-DT of >12 mo.	Strong
ADT = androgen deprivation therapy; HIFU = high-intensity focused ultrasound; PCa = prostate cancer; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; RP = radical prostatectomy; SRT = salvage radiotherapy.	

Table 2 – Definition of high and low volume, and risk in CHAARTED [54–56] and LATITUDE [57] based upon imaging with bone scan and CT scan.

	High	Low
CHAARTED (volume)	≥4 Bone metastasis including ≥1 outside vertebral column or pelvis and/or visceral metastasis	Not high
LATITUDE (risk)	≥2 High-risk features of: ≥3 Bone metastasis Visceral metastasis ≥ISUP grade 4	Not high
CT = computed tomography; ISUP = International Society of Urological Pathology.		

have shown that the mean testosterone level after surgical castration is 15 ng/dl (0.52 nmol/l) [61], and testosterone levels <20 ng/dl (<0.69 nmol/l) are associated with improvement in outcomes compared with men who only reach a level of between 20 and 50 ng/dl (0.69–1.74 nmol/l) [62,63]. 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 and avoid the physical and psychological discomfort associated with orchiectomy [64]. At the initiation of LHRH agonists, antiandrogen therapy [65] should be considered to suppress the “testosterone surge” phenomenon. It is usually continued for about 4 wk. LHRH antagonists are also available [66]. 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.

3.2. Intermittent ADT

SWOG 9346 is the largest trial addressing intermittent androgen deprivation (IAD) in M1b patients [67]. Out of 3040 patients screened, only 1535 met the inclusion criteria. This highlights that, at best, only 50% of M1b patients can be expected to be candidates for IAD, that is, the best PSA responders. This was a noninferiority trial leading to inconclusive results: the actual upper limit was above the prespecified 90% upper limit of 1.2 (hazard ratio [HR]: 1.1; confidence interval [CI]: 0.99–1.23), the pre-specified noninferiority limit was not achieved, and the results did not show significant inferiority for any treatment arm. However, based on this study, inferior survival with IAD cannot be ruled out completely. Three independent reviews [68–70] and a meta-analysis [71] have evaluated the clinical efficacy of IAD. All these reviews included eight randomised controlled trials (RCTs), of which only three were conducted in patients with M1 disease only. These reviews and the meta-analysis came to the conclusion that there was no statistically significant difference in OS or CSS between IAD and continuous androgen deprivation whilst highlighting the limitations of most trials, and suggested a

cautious interpretation of the noninferiority results [72]. There is a trend favouring IAD in terms of treatment-related side effects such as hot flushes, but no sustained improvement in QoL [73,74]. However, combination therapies with their proven survival benefits have all been studied with continuous ADT, and this has further limited the role of IAD.

3.3. Combined androgen blockade

The use of earlier nonsteroidal antiandrogens (flutamide, nilutamide, and bicalutamide) in combination with ADT produced a small statistical improvement in survival, although of questionable clinical benefit [75]. Modern androgen receptor-targeted agents (ARTAs; enzalutamide and apalutamide) plus abiraterone acetate, a CYP17 inhibitor (given in combination with continuous prednisone/prednisolone), also target the androgen axis, but much more effectively (Table 3). The addition of these agents improves clinical outcomes significantly, with no convincing evidence of differences in outcome when analysed by the volume of disease or risk. All secondary objectives such as PFS, time to radiographic progression, time to pain, and time to chemotherapy, were positive and in favour of the combination [57,76–79]. The majority of patients treated had de novo metastatic disease, and the evidence is most compelling in this situation. However, it may still be considered for men progressing after local therapy. The most convincing data are found in ENZAMET, where almost half of the patients had previous local therapy.

3.4. ADT combined with chemotherapy

Three large RCTs were conducted [53,55,80]. All trials compared between ADT alone as the standard of care and ADT combined with immediate docetaxel (75 mg/m² every 3 wk; within 3 mo of ADT initiation). The primary objective in all three studies was OS. The key findings are summarised in Table 4. In the three trials, toxicity was mainly haematological, with approximately 12–15% grade 3–4 neutropenia and 6–12% grade 3–4 febrile neutropenia. Concomitant use of the granulocyte colony-stimulating factor (G-CSF) receptor was shown to be helpful, and its use should be based on available guidelines [81]. A Cochrane systematic review and meta-analysis, which included these three trials, showed that the addition of docetaxel to the standard of care improved survival [82]. The HR of 0.77 (95% CI: 0.68–0.87; $p < 0.0001$) translates into an absolute improvement in 4-yr survival of 9% (95% CI: 5–14). Docetaxel in addition to the standard of care also improves failure-free survival, with an HR of 0.64 (95% CI: 0.58–0.70; $p < 0.0001$) translating into a reduction in absolute 4-yr failure rates of 16% (95% CI: 12–19). Lastly, whether the addition of an androgen-targeted agent plus docetaxel plus ADT adds further benefit is currently not clear as longer follow-up is needed [83]. However, it is clear that all men presenting with metastatic disease should be offered a form of combination treatment unless there is a clear contraindication.

Table 3 – Benefits of combined androgen blockade using androgen receptor–targeted agents.

	STAMPEDE arm G [186]		LATITUDE [57]		ENZAMET [78]		TITAN [77]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P	ADT + older antagonist ± docetaxel (SOC)	ADT + enzalutamide ± docetaxel	ADT + placebo	ADT + apalutamide
N	957	960	597	602	562	563	527	525
Newly diagnosed N+ (%)	20	19	0	0			0	0
Newly diagnosed M+ (%)	50	48	100	100	58	58	100	100
Primary objective	OS		OS		OS		OS	
			Radiographic PFS				Radiographic PFS	
Median follow-up (mo)	40		30.4		34		30.4	
3-yr OS	83%	(ADT + AA + P)	66% (ADT + AA + P)	49% (ADT + placebo)	3-yr survival: 80% (ADT + enzalutamide) 72% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI)	0.63	(0.52–0.76)	0.62	(0.51–0.76)	0.67	(0.52–0.86)	0.67	(0.51–0.89)

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; n = number of patients; OS = overall survival; P = prednisone; PFS = progression-free survival; SOC = standard of care.

Table 4 – Key findings: hormonal treatment combined with chemotherapy in men presenting with metastatic disease.

	STAMPEDE [80]		GETUG [53]		CHAARTED [55]	
	ADT	ADT + docetaxel + P	ADT	ADT + docetaxel	ADT	ADT + docetaxel
n	1184	592	193	192	393	397
Newly diagnosed M+ (%)	58	59	75	67	73	73
Key inclusion criteria	Patients scheduled for long-term ADT - Newly diagnosed M1 or N+ situations - Locally advanced (at least two of cT3, cT4, ISUP grade ≥4, PSA ≥40 ng/mL) - Relapsing locally treated disease with PSA >4 ng/mL and PSA-DT <6 mo, or PSA >20 ng/mL, or nodal or metastatic relapse		Metastatic disease Karnofsky score ≥70%		Metastatic disease ECOG PS 0, 1, or 2	
Primary objective	OS		OS		OS	
Median follow-up (mo)	43		50		53	
HR (95% CI)	0.78 (0.66–0.93)		1.01 (0.75–1.36)		0.72 (0.59–0.89)	
M1 only						
N	1086		NR		NR	
HR (95% CI)	0.76 (0.62–0.92)		NR		NR	

ADT = androgen deprivation therapy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; ISUP = International Society of Urological Pathology; n = number of patients; NR = not reported; OS = overall survival; P = prednisone; PSA = prostate-specific antigen; PSA-DT = prostate-specific androgen doubling time.
*HV indicates either visceral metastases or more than four bone metastases with at least one outside the spine and pelvis.

3.5. Treatment of the primary tumour in newly diagnosed metastatic disease

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial [84]. A total of 432 patients were randomised to ADT alone or ADT plus external beam radiation therapy (EBRT) to the prostate. OS was not significantly different, but the median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]). The STAMPEDE trial also evaluated 2061 men with metastatic hormone-sensitive PCa (mHSPC) who were randomised to ADT alone versus ADT plus RT to the prostate only. This trial confirmed that RT to the primary tumour did not improve OS in

unselected patients [58]. However, following the results from CHARTED, and prior to analysing the data, the original screening investigations were retrieved and patients were categorised as having low- or high-volume disease. In the low-volume subgroup (n = 819), there was a significant OS benefit by the addition of prostate RT. Therefore, RT of the prostate in patients with low-volume metastatic disease should be considered. It is not clear whether these data can be extrapolated to RP as local treatment; results of on-going trials are awaited.

In a recent systematic review and meta-analysis including the above two RCTs, the authors found that there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04,

Table 5 – Guidelines for hormonal treatment of metastatic prostate cancer.

Recommendations	Strength rating
Offer immediate systemic treatment with ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, and ureteral obstruction) to M1 symptomatic patients.	Strong
Offer LHRH antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment also to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side effects, provided that the patient is monitored closely.	Weak
Offer short-term administration of an older-generation AR antagonist to M1 patients starting LHRH agonist to reduce the risk of the “flare-up” phenomenon.	Weak
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate RT to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
ADT = androgen deprivation therapy; AR = androgen receptor; CHAARTED = Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; LHRH = luteinising hormone-releasing hormone; RT = radiotherapy.	

$p = 0.195$; heterogeneity chi-square = 0.08, degree of freedom = 1, $p = 0.78$) [85]. However, there was a difference in the effect of metastatic burden on survival, with an absolute improvement of 7% in 3-yr survival in men who had four or fewer bone metastases.

3.6. Metastasis-directed therapy

In patients relapsing after a local treatment and a limited number of metastases, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. A randomised phase II trial evaluated metastasis-directed therapy (MDT) versus surveillance in men with oligorecurrent PCa. Oligorecurrence was defined as three or fewer lesions on PET-choline only. The sample size was small with 62 patients, and about half of them had nodal disease in the pelvis only. ADT-free survival was the primary end point, which was longer with MDT than with surveillance [86]. Recently, in a phase II study [87], 54 men were randomised 2:1 to stereotactic ablative radiotherapy (SABR) or observation. Patients had one to three asymptomatic metastases by conventional imaging but subsequently underwent a PSMA PET scan, although this information was not shared with the treating team. The primary outcome was progression at 6 mo by PSA level increase, progression detected by conventional imaging, symptomatic progression, ADT initiation for any reason, or death. Progression at 6 mo occurred in seven of 36 patients having SABR and 11 of 18 undergoing observation ($p = 0.005$). Sixteen of 36 participants treated with SABR had baseline PET-avid lesions that were not included in the treatment fields. The proportion of men with no untreated lesions who had progression at 6 mo was 1 of 19 (5%; 95% CI: 0–26.8) compared with 6 of 16 (38%; 95% CI: 18.5–61.5) for those with any untreated lesions ($p = 0.03$). However, at this stage, it is unclear whether the improved outcomes are related to complete consolidation of detectable disease or the volume

of disease. In addition, there remain no data to suggest an improvement in OS. See Table 5 for treatment recommendations.

3.7. Follow-up during hormonal treatment

The main objectives of follow-up in men on ADT are to ensure treatment compliance, monitor treatment response and side effects, and 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 symptomatic response and the change in serum PSA level [88]. In general, asymptomatic patients with a stable PSA level do not require further imaging, although care needs to be taken in patients with very dysplastic cancers when PSA may not reflect tumour progression. Table 6 summarises the guidelines for follow-up during hormonal therapy. New-onset bone pain requires imaging, 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 [89] that are later confirmed. Suspicion of disease progression indicates the need for additional imaging modalities guided by symptoms and possible subsequent treatments.

ADT reduces bone mineral density (BMD) and increases the risk of fractures [90]. It is recommended that BMD and the levels of serum vitamin D and calcium should be measured at the commencement of ADT and every 2 yr

Table 6 – Guidelines for follow-up during hormonal treatment.

Recommendations	Strength rating
The follow-up strategy must be individualised based on the stage of disease, prior symptoms, prognostic factors, and the treatment given.	Strong
In patients with M0 disease, schedule follow-up at least every 6 mo. As a minimum requirement, include a disease-specific history, PSA determination, as well as liver and renal function in the diagnostic work-up.	Strong
In patients with stage M1 disease on ADT alone, schedule follow-up every 3–6 mo. As a minimum requirement, include an initial FRAX-score assessment, disease-specific history, digital rectal examination, serum PSA, haemoglobin, serum creatinine, and ALP measurements in the diagnostic work-up. The testosterone level should be checked, especially during the 1st year. Pay attention to symptoms associated with metabolic syndrome as a side effect of ADT. Lipid profiles and HbA1c levels should be checked and treated if abnormal.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level of <50 ng/dl (<1 ml/l).	Strong

ADT = androgen deprivation therapy; ALP = alkaline phosphatase; FRAX = Fracture Risk Assessment Tool; PCa = prostate cancer; PSA = prostate-specific antigen.

Table 7 – Combined androgen blockade for nmCRPC.

	SPARTAN [98,101] Apalutamide 240 mg o.d. vs placebo	PROSPER [99,102] enzalutamide 160 mg o.d. vs placebo	ARAMIS [100,103] Darolutamide 600 mg b.d. vs placebo
<i>n</i>	806:401	933:468	955:554
Median PSA-DT (mo)	4.4	3.8	4.4
Metastasis-free survival (mo)	40.5 vs 16.2 (<i>p</i> < 0.001)	36.6 vs 14.7 (<i>p</i> < 0.001)	40.4 vs 18.4 (<i>p</i> < 0.0001)
Overall survival (mo)	73.9 vs 59.9 (HR 0.78 [0.64–0.96], <i>p</i> = 0.0161)	67.0 vs 56.3 (HR 0.73 [0.61–0.89], <i>p</i> = 0.001)	NR vs NR (HR 0.69 [0.53–0.88], <i>p</i> = 0.003)

HR = hazard ratio; *n* = number of patients; nmCRPC = nonmetastatic castration-resistant prostate cancer; NR = not reached; o.d. = once a day; PSA-DT = prostate-specific antigen doubling time.

[91]. Treatment should be individualised; however, for men with a BMD T score of <−2.5 and one or more risk factors, or with hip and vertebral fractures, the use of bisphosphonates or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors should be discussed, but at the osteoporotic registered dose and not at the CRPC dose intensity. Specialists should also screen patients for the development of metabolic sequelae associated with ADT such as alterations in lipid profiles and decreased insulin sensitivity [92]. Treatment strategies to reduce the risk of diabetes and cardiovascular disease are recommended [93]. Patients should be given advice on modifying their lifestyle (eg, diet, exercise, and smoking cessation) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension.

4. Castration-resistant PCa

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:

- 1 Biochemical progression: three consecutive rises in PSA 1 wk apart, resulting in two 50% increases over the nadir, and PSA > 2 ng/mL
- 2 Radiological progression: the appearance of new lesions—either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumours [34,94]

4.2. Management of CRPC

Selection of treatment for CRPC is multifactorial and in general depends on the following:

- 1 Previous treatment for HSPC and CRPC
- 2 Quality of response and pace of progression on previous treatment
- 3 Known cross resistance between androgen-targeted agents (ATAs)
- 4 Known genetic alterations
- 5 Known histological variants and DNA repair deficiency
- 6 Local approval status of drugs and reimbursement situation

Clinical parameters of aggressive disease such as a short response to mHSPC therapy, high tumour burden, rapid pace of progression, visceral metastases, and poor genomics (p53, RB, myc) should prompt the use of chemotherapy or clinical trials rather than ATA [95].

4.2.1. Nonmetastatic CRPC

Frequent PSA testing for men on treatment with ADT has resulted in earlier detection of biochemical progression. Of these men, approximately one-third will develop bone metastases detectable on bone scan within 2 yr [96].

In men with CRPC and no detectable clinical metastases using bone and CT scans, baseline PSA level, PSA velocity, and PSA-DT (<10 mo) have been associated with the time to first bone metastasis, bone metastasis-free survival, and OS [96,97]. Three large randomised controlled phase III trials, SPARTAN [98], PROSPER [99], and ARAMIS [100], evaluated

metastasis-free survival as the primary end point in patients with nonmetastatic CRPC (M0 CRPC) treated with the addition of a modern antiandrogen to ADT. The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ 10 mo were included. Results are shown in Table 7. All three studies confirmed improvement in the primary end point and, following further follow-up, have also been confirmed to improve OS [101–103].

Men with more slowly developing nonmetastatic CRPC (PSA-DT >10 mo) remain candidates for monitoring rather than intervention.

4.2.2. Metastatic CRPC

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [104,105]. However, in the absence of prospective data, the modest potential benefits of continuing agonists or antagonists to suppress testosterone to the castrate level outweigh the minimal risks of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression (Table 8).

4.2.2.1. First-line treatment of metastatic CRPC

4.2.2.1.1. Abiraterone. Abiraterone was evaluated in 1088 chemo-naïve, asymptomatic or mildly symptomatic, mCRPC

patients in the phase III trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone 10 mg daily [104]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1, and asymptomatic or mildly symptomatic disease. OS and radiographic PFS (rPFS) were the coprimary 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, $p = 0.0033$) [106,107]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly of grade 1–2. A subset analysis of this trial showed the drug to be equally effective in an elderly population (>75 yr) [108].

4.2.2.1.2. Enzalutamide. Enzalutamide has also been compared with bicalutamide 50 mg/d in a randomised double-blind phase II study (TERRAIN) [109] showing a significant improvement in PFS (15.7 vs 5.8 mo, HR: 0.44, $p < 0.0001$) in favour of enzalutamide. A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide with placebo [110]. Men with visceral metastases were eligible, but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naïve mCRPC population of 1717 men and showed a significant improve-

Table 8 – Guidelines for management of castration-resistant prostate cancer.

Recommendations	Strength rating
Life-prolonging treatments of castration-resistant disease	
Ensure that testosterone levels are confirmed to be <50 ng/dl, before diagnosing castration-resistant PCa (CRPC).	Strong
Counsel, manage, and treat patients with mCRPC in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and previous treatment for HSPC (in alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong
Nonmetastatic castrate-resistant disease	
Offer apalutamide, darolutamide, or enzalutamide in addition to ADT to patients with M0 CRPC who have not been exposed to ATA previously and with a high risk of developing metastasis (PSA-DT <10 mo) to prolong time to metastases and improve OS.	Strong
Metastatic castration-resistant disease	
Offer docetaxel 75 mg/m ² every 3 wk to patients with mCRPC who are candidates for cytotoxic therapy.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, and radium-223 ^a .	Strong
Base further treatment decisions of mCRPC on pretreatment performance status, response to previous treatment, symptoms, comorbidities, extent of disease, and patient preference.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 mo of treatment with abiraterone or enzalutamide.	Strong
Supportive care of castration-resistant disease	
Offer bone-protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium, and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as RT and adequate use of analgesics.	Strong
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.	Strong

ADT = androgen deprivation therapy; ATA = androgen-targeted agents; CRPC = castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PCa = prostate cancer; PSA-DT = PSA doubling time; RT = radiotherapy.

^a Radium-223 should be offered only to patients progressing after docetaxel and one ATA.

ment in both coprimary end points: rPFS (HR: 0.186, CI: 0.15–0.23, $p < 0.0001$) and OS (HR: 0.706, CI: 0.6–0.84, $p < 0.001$). The most common clinically relevant adverse events were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men aged >75 yr [111] as well as in those with or without visceral metastases [112]. However, for men with liver metastases, there seems to be no clear evidence of a discernible benefit [112,113]. With extended follow-up and final analysis, the benefit in OS and rPFS were confirmed [114].

4.2.2.1.3. Docetaxel. A significant improvement in median survival of 2–2.9 mo has been shown with docetaxel-based chemotherapy compared with mitoxantrone plus prednisone therapy [115,116]. The standard first-line chemotherapy is docetaxel 75 mg/m², 3 weekly, combined with prednisone 5 mg twice a day, up to 10 cycles. Independent prognostic factors, including visceral metastases, pain, anaemia (haemoglobin <13 g/dl), bone scan progression, and prior estramustine, may help stratify the response to docetaxel. Age by itself is not a contraindication to docetaxel [117], but attention must be paid to careful monitoring and comorbidities [118]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m² every 2 wk seems to be well tolerated with fewer grade 3–4 adverse events and a prolonged time to treatment failure [119].

4.2.2.1.4. Sipuleucel-T. In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [97]. After a median follow-up of 34 mo, the median survival was 25.8 mo in the sipuleucel-T group compared with 21.7 mo in the placebo group, with an HR of 0.78 ($p = 0.03$). No PSA decline was observed, and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related grade 1–2 adverse events in the sipuleucel-T group, but the same grade 3–4 adverse events in both arms. Sipuleucel-T is not available in Europe (and its licence has lapsed).

4.2.2.2. Second-line treatment for mCRPC and sequencing. All patients who receive treatment for mCRPC will eventually progress.

4.2.2.2.1. Cabazitaxel. Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III 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 [120]. Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) plus prednisone (10 mg/d). OS was the primary end point, which was significantly longer with cabazitaxel (median: 15.1 vs 12.7 mo, $p < 0.0001$). There was also a significant improvement in PFS (median: 2.8 vs 1.4 mo, $p < 0.0001$), objective RECIST response (14.4% vs 4.4%, $p < 0.005$), and PSA response rate (39.2% vs 17.8%, $p < 0.0002$). Treatment-

associated World Health Organization grade 3–4 adverse events developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs 47.3%, $p < 0.0002$) but also nonhaematological (57.4% vs 39.8%, $p < 0.0002$) toxicity [121]. In two postmarketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m² cabazitaxel was not inferior to 25 mg/m², but less toxic. Therefore, the lower dose should be preferred [122,123]. Cabazitaxel should preferably be given with prophylactic G-CSF and should be administered by physicians with expertise in handling neutropenia and sepsis [124].

4.2.2.2.2. Abiraterone acetate after prior docetaxel. Positive results of the large phase III trial COU-AA-301 were reported after a median follow-up of 12.8 mo [125] and confirmed with further follow-up [126]. 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. After a median follow-up of 20.2 mo, the 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 the secondary objectives were in favour of abiraterone (PSA, radiological tissue response, time to PSA, or objective progression). The incidence of the most common grade 3–4 adverse events did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly those of grade 1–2 (fluid retention, oedema, and hypokalaemia).

4.2.2.2.3. Enzalutamide after docetaxel. The planned (and final) interim analysis of the AFFIRM study was published in 2012 [127]. 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 about 30% of the patients. 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, the 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 to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. Enzalutamide was active also in patients with visceral metastases.

All the 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 adverse events in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared with none in the placebo arm.

4.2.2.2.4. Radium-223. The only bone-specific drug that is associated with a survival benefit is the α -emitter radium-223. In a large phase III trial (ALSYMPCA), 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo, plus the standard of care. The primary end point was OS. Radium-223 significantly improved median OS by 3.6 mo (HR: 0.70, $p < 0.001$) and was also associated with prolonged time to first skeletal event, improvement in pain scores, and improvement in QoL [128]. The associated toxicity was mild and, apart from slightly more haematological toxicity and diarrhoea with radium-223, it did not differ significantly from that in the placebo arm [128]. Radium-223 was effective and safe irrespective of whether patients were pretreated with docetaxel or not [129]. Owing to bone safety concerns, the use of radium-223 was recently restricted to after docetaxel and at least one ARTA [130]. In particular, the use of radium-223 in combination with abiraterone acetate plus prednisolone showed significant safety risks related to nonpathological fractures and more deaths. This was particularly striking in patients without the concurrent use of antiresorptive agents [131].

4.2.2.2.3. Treatment after docetaxel and one line of hormonal treatment for mCRPC. For men progressing quickly on androgen receptor-targeted therapy (<12 mo), it is now clear that cabazitaxel is the treatment of choice with the best supporting data. The CARD trial, an open-label randomised phase II trial, evaluated cabazitaxel after docetaxel and one line of ATA (either abiraterone plus prednisolone or enzalutamide) [132]. It included patients progressing in <12 mo on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled the rPFS and reduced the risk of death by 36% versus another ATA. The rPFS with cabazitaxel remained superior regardless of the ATA sequence and whether docetaxel was given before, or after, the first ATA.

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open for patients who have a >12 mo response to first-line abiraterone or enzalutamide for mCRPC [133]. Either radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options. In general, subsequent treatments in unselected patients are expected to have fewer benefits than with earlier use [134,135], and there is evidence of cross resistance between enzalutamide and abiraterone [136,137].

4.2.2.3.1. Poly (ADP ribose) polymerase inhibitors. Poly (ADP ribose) polymerase (PARP) inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one novel hormonal agent, and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes (*BRCA1/2*, *ATM*, Fanconi's anaemia genes, and *CHEK2*), showed an 88% response rate [138].

Following docetaxel, a randomised phase II trial, which assigned 142 patients to receive olaparib and abiraterone

($n = 71$) or placebo and abiraterone ($n = 71$), demonstrated a clinical benefit regardless of the homologous recombination deficiency status. Combination treatment is toxic, with serious side effects reported in 34% of the olaparib/abiraterone group versus 18% in the placebo/abiraterone group [139].

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib with an alternative ATA in mCRPC with alterations in one or more of any qualifying genes with a role in HRR and progression on an ATA and docetaxel. An investigational clinical trial assay, based on the FoundationOne CDx next-generation sequencing test, was used to prospectively identify patients with qualifying deleterious or suspected deleterious alterations in at least one of the 15 prespecified genes selected for their direct or indirect role in HRR [140]. Radiographic PFS by a blinded independent central review in the overall cohort favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). The interim results for OS demonstrated improved nonsignificant survival among men with *BRCA1/2* or *ATM* mutations (cohort A; HR: 0.64, 95% CI: 0.43–0.97) as well as in men with any HRR alteration (*BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*; cohort B; HR: 0.67, 95% CI: 0.49–0.93). Of note, patients in the physician's choice of enzalutamide/abiraterone arm who progressed, 80.6% in cohort A and 84.6% in cohort B, crossed over to receive olaparib. When looking specifically at cohort B patients, there was no advantage to olaparib in the rPFS by the blinded independent central review (HR: 0.88, 95% CI: 0.58–1.36) or in OS (HR: 0.73, 95% CI: 0.45–1.23); however, there was a benefit to olaparib for rPFS by investigator assessment (HR: 0.60, 95% CI: >0.39 –0.93).

The most common adverse events were anaemia (46.1% vs 15.4%), nausea (41.4% vs 19.2%), decreased appetite (30.1% vs 17.7%), and fatigue (26.2% vs 20.8%) for olaparib versus enzalutamide/abiraterone. Among patients receiving olaparib, 16.4% discontinued treatment secondary to an adverse event, compared with 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared with 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first published trial to show a benefit for genetic testing and precision medicine for mCRPC. Olaparib and rucaparib are both licenced by the U.S. Food and Drug Administration (FDA) but not currently by the European Medicines Agency (EMA). The olaparib approval is for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The rucaparib approval is for patients with a deleterious *BRCA* mutation (germline and/or somatic) associated mCRPC who have been treated with ATA and a taxane-based chemotherapy. This is based upon data from the on-going Triton 2 study [141]. Both agents offer an exciting new opportunity to tailor therapy based on the mutation profile (mainly *BRCA1/2*) contained within a

tumour or germline. However, it should be noted that only 18% of screened patients were eligible.

4.2.2.3.2. Gallium PSMA therapy. The increasing use of PSMA PET as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope, which accumulates where the tumour is demonstrated (theranostics) [142]. Therefore, after identification of the target, usually with diagnostic ^{68}Ga -labelled PSMA, therapeutic radiopharmaceuticals labelled with beta (lutetium-177 or yttrium-90)- or alpha (actinium-225)-emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported with the most robust data is Lu-PSMA-617. The first patient was treated in 2014, and early clinical studies evaluating the safety and efficacy of Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [143]. Data from uncontrolled prospective phase II trials have been published [144,145], reporting high response rates, with low toxic effects. The first randomised trial [146] compared Lu-PSMA-617 with cabazitaxel in men with docetaxel-progressing mCRPC. Patients were screened with a PSMA PET scan and a fluorodeoxyglucose PET scan. A total of 200 men were randomly assigned 1:1 to Lu-PSMA every 6 wk up to six cycles or to cabazitaxel 20 mg/m² every 3 wk for up to 10 cycles. The primary end point of a decline of $\geq 50\%$ in PSA level showed a 66% response in the Lu-PSMA arm versus 37% in the cabazitaxel arm ($p < 0.0001$). A preliminary analysis of PSA PFS found that Lu-PSMA delayed disease progression by 31% compared with cabazitaxel. PFS data are not yet mature, but grade 3 or 4 complications were more common in the cabazitaxel arm.

4.2.2.4. Follow-up during treatment. Baseline examinations should include a medical history, clinical examination, as well as baseline blood tests (PSA, testosterone, full blood count, renal function, liver function tests, and ALP), bone scan, and CT of the chest, abdomen, and pelvis [147]. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR. Flares, PSMA upregulation, and discordant results compared with PSA response or progression on ARTAs have been described [148]. PSA alone is not reliable enough [149] for monitoring disease activity in advanced CRPC, since metastases may develop in men without rising PSA [150]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements, and clinical benefit in assessing men with CRPC [116]. A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating 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 [147]. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression, and clinical deterior-

ation) should be fulfilled to stop and switch treatment. For trial purposes, the updated PCWG3 criteria put more weight on the importance of documenting progression in existing lesions, and introduced the concept of “no longer clinically benefiting” to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [151]. These recommendations also seem to be valid for clinical practice outside trials.

4.2.2.4.1. Symptomatic management in metastatic CRPC. CRPC is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, geriatricians, nurses, psychologists, and social workers [152,153]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue, and depression.

4.2.2.4.2. Common complications due to bone metastases. Many patients with mCRPC have painful bone metastases, and ADT causes bone demineralisation. EBRT is highly effective, even as a single fraction [154,155]. A single infusion of a third-generation bisphosphonate could be considered when RT is not available [156]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures, and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [157]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [158,159]. Impending spinal cord compression is an emergency. It must be recognised early, and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and emergency MRI performed. Consultation with a systematic neurosurgery or orthopaedic surgeon should be planned to discuss a possible decompression, followed by EBRT [160]. Otherwise, EBRT with or without systemic therapy is the treatment of choice.

4.2.2.4.3. Bisphosphonates. Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SREs). This study was conducted when no active anticancer treatments, but for docetaxel, was available. A total of 643 patients who had CRPC [161] 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 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 than the placebo group (44% vs 33%, $p = 0.021$) and in particular fewer pathological fractures (13.1% vs 22.1%, $p = 0.015$). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen with bisphosphonates in any prospective trial.

4.2.2.4.4. RANK ligand inhibitors. Denosumab is a fully human monoclonal antibody directed against the RANK 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, $p = 0.028$) [162]. This benefit did not translate into a survival difference (43.9 compared with 44.8 mo, respectively), and neither the FDA or the EMA has approved denosumab for this indication.

The efficacy and safety of denosumab ($n = 950$) compared with zoledronic acid ($n = 951$) in patients with mCRPC treated with 4-weekly injections was assessed in a phase III trial [163]. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by the time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 versus 17.1 mo (HR: 0.82, $p = 0.008$). Both urinary N-telopeptide and bone-specific ALP were significantly suppressed in the denosumab arm compared with the zoledronic acid arm ($p < 0.0001$ for both).

The potential toxicity (eg, osteonecrosis of the jaw and hypocalcaemia) of these drugs must always be kept in mind (5–8.2% in M0 CRPC and mCRPC, respectively) [162,164]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery, or dental infection [165]. In addition, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial (1 vs 2 yr with denosumab) [166], but this was not statistically significant when compared with zoledronic acid [163]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab as well as zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy [167]. Hypocalcaemia should be identified and prevented during treatment with bone-protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively [164]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks, and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU equivalent) are recommended in all patients, unless there is demonstrated hypercalcaemia [164,168].

5. QoL outcomes in PCa

Living longer with PCa does not necessarily equate to living well [169]. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa [170]. Cancer impacts the wider family, and cognitive behavioural therapy can help reduce depression, anxiety, and stress in caregivers [171]. Radical treatment for PCa can negatively impact long-term QoL (eg, sexual, urinary, and bowel dysfunction), as can ADT used in short- or long-term treatment, for example, sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae, and increased cardiovascular and bone fracture risk [172]. Direct symptoms from advanced or metastatic

cancer, for example, pain, hypercalcaemia, spinal cord compression, and pathological fractures, also affect health adversely [173,174]. Men's QoL including domains such as sexual, urinary, and bowel function is worse after treatment for PCa than noncancer controls [175,176]. See Table 9 for recommendations.

5.1. Men undergoing local treatments

The results of the Prostate Testing for Cancer and Treatment (ProtecT) trial ($n = 1643$ men) reported no difference in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30–assessed global QoL, up to 5 yr of follow-up, in 50–69-yr-old men with T1-T2 disease randomised for treatment with active monitoring (AM), RP, or RT with 6 mo of ADT [177]. However, Expanded Prostate Cancer Index Composite (EPIC) urinary summary scores (at 6 yr) were worse in men treated with RP than in men receiving AM or RT (88.7 vs 89.0 vs 91.4), as were urinary incontinence (80.9 vs 85.8 vs 89.4) and sexual summary, function, and bother scores (32.3 vs 40.6 vs 41.3 for sexual summary, 23.7 vs 32.5 vs 32.7 for sexual function, and 51.4 vs 57.9 vs 60.1 for sexual bother) at 6 yr of follow-up. Minimal clinically important differences for the 50-item EPIC questionnaire are not available. For men receiving RT with 6 mo of ADT, EPIC bowel scores were poorer than those for men receiving AM and RP in all domains: function (90.8 vs 92.3 vs 92.3), bother (91.7 vs 94.2 vs 93.7), and summary (91.2 vs 93.2 vs 93.0) at 6 yr of follow-up in the ProtecT trial.

With respect to brachytherapy cancer-specific QoL outcomes, one small RCT ($n = 200$) evaluated bilateral nerve-sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsening of physical functioning as well as irritative urinary symptomatology in 20% of brachytherapy patients at 1 yr of follow-up. However, there were no significant differences in EORTC QLQ-C30/PR-25 scores at 5 yr of follow-up when comparing with pretreatment values [178]. In a subsequent study by the same group comparing bilateral nerve-sparing robotic-assisted RP with brachytherapy ($n = 165$), improved continence was noted with brachytherapy in the first 6 mo but potency rates were lower for up to 2 yr [179]. These data and a synthesis of 18 randomised and nonrandomised studies in a systematic review involving 13 604 patients are the foundation of the following recommendations [180].

5.2. Men undergoing systemic treatments

Providing supervised aerobic and resistance exercise training of a moderate intensity improves the role of EORTC QLQ-C30 (adjusted mean 15.8; 95% CI: 6.6–24.9) and cognitive domain outcomes (adjusted mean 11.4; 95% CI: 3.3–19.6) as well as symptom scales for fatigue (adjusted mean 11.0; 95% CI: 20.2–1.7), nausea (adjusted mean 4.0; 95% CI: 7.4–0.25), and dyspnoea (adjusted mean 12.4; 95% CI: 22.5–2.3) for up to 3 mo in men treated with ADT [181]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9;

Table 9 – Guidelines for quality of life in men undergoing local and systemic treatments.

Recommendations	Strength rating
Advise patients eligible for AS that global QoL with AS is equivalent, for up to 5 yr, to that with RP or EBRT.	Strong
Discuss with patients the negative impact of surgery on urinary and sexual function, as well as the negative impact of RT on bowel function.	Strong
Inform patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at 1 yr but not after 5 yr.	Weak
Offer men with T1-T3 disease specialist nurse-led multidisciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support, and positive lifestyle changes after any radical treatment.	Strong
Advise men on ADT to maintain a healthy weight and diet, stop smoking, and have yearly screening for diabetes and hypercholesterolaemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer 12 wk of supervised (by trained exercise specialists) combined aerobic and resistance exercise to men on ADT.	Strong
Use the FRAX tool to guide monitoring and treatment of bone mineral density in men on long-term ADT.	Strong
Offer DEXA scanning to men starting on long-term ADT, to assess bone mineral density.	Strong
ADT = androgen deprivation therapy; AS = active surveillance; DEXA = dual emission x-ray absorption; EBRT = external beam radiotherapy; FRAX = Fracture Risk Assessment Tool; QoL = quality of life; RP = radical prostatectomy; RT = radiotherapy.	

95% CI: 3.7–14.2) in men on long-term ADT [182,183]. These findings are supported by a systematic review that reported improvements up to 12 wk in cancer-specific QoL in a meta-analysis of high-quality trials (standardised mean difference 0.33; 95% CI: 0.08–0.58) [184].

In case dietary intake is not adequate, vitamin D and calcium supplementation should be offered, as there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [185].

6. Conclusions

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

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