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RESEARCH ARTICLE

Consensus on management of castration-resistant prostate cancer on behalf of the Urological Tumours Working Group (URONCOR) of the Spanish Society of Radiation Oncology

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Abstract

Background The knowledge in the field of castration-resistant prostate cancer (CRPC) is developing rapidly, with emerging new therapies and advances in imaging. Nonetheless, in multiple areas there is still a lack of or very limited evidence, and clear guidance from clinicians regarding optimal strategy is required.

Methods A modified Delphi method, with 116 relevant questions divided into 7 different CRPC management topics, was used to develop a consensus statement by the URONCOR group.

Results A strong consensus or unanimity was reached on 93% of the proposed questions. The seven topics addressed were: CRPC definition, symptomatic patients, diagnosis of metastasis, CRPC progression, M0 management, M1 management and sequencing therapy, and treatment monitoring.

Conclusions The recommendations based on the radiation oncology experts' opinions are intended to provide cancer specialists with expert guidance and to standardise CRPC patient management in Spain, facilitating decision-making in different clinically relevant issues regarding CRPC patients.

Keywords Castration-resistant prostate cancer · Radiation oncology · Consensus · Delphi · Management · Metastasic · Therapeutics · Oligometastasic prostate cancer

Introduction

Prostate cancer is the second most common cancer in men worldwide. In recent years, in Europe as in Spain, it has been the most frequent (360,000 cases diagnosed in the EU-27 in 2012 and 33,370 new cases in Spain in 2015) [1], with the incidence presenting a significant increase after the fifth decade. In 2012 it was the malignancy with the highest incidence and prevalence in Spain (12.9%) [2, 3]. Data from population-based cancer registries in Spain have shown an improvement in prostate cancer prognosis, with 84.5%

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5-year relative survival (95% CI 83.6–85.6%) [4]. However, this survival rate drops rapidly among the older age patients with an advanced stage of the disease at diagnosis [5].

Although most patients initially respond to medical radiation or surgical therapy, around 10–20% of prostate cancer patients develop a castration-resistant prostate cancer (CRPC), within 5 years of follow-up [6]. CRPC is a heterogeneous disease, with metastases present in over 84% of patients [7], deterioration in the quality of life and shorter survival compared with castration-sensitive patients [6, 8].

Treatment for CRPC has improved considerably in these recent years, with several agents extending life, including androgen-receptor pathway therapies (enzalutamide, abiraterone) [9, 10], autologous cellular immunotherapy (sipuleucel-T, not available in Europe) [11], radium-223 [12] and cabazitaxel [13]. Despite these new emerging therapies, there is an absence of face-to-face comparative studies between therapeutic options. Therefore, there is still controversy on how to sequence or combine these therapies in order to provide the greatest benefits to the patients [14].

Furthermore, with the availability of new imaging tools the diagnoses of metastasis and progression in CPRC is constantly evolving and there are no clear recommendations on when to initiate imaging or the testing frequency in clinical practice. The usefulness of new imaging technique in advanced prostate cancer and its clinical benefit will be answered in trials that directly assess these techniques.

To address this issue, the SEOR Urological Tumour Working Group (URONCOR) consulted a working panel of 25 radiation oncologist experts in order to provide a consensus on many controversial aspects in CRPC management, including the definition of CRPC, aspects relating to symptomatic patients, diagnosis of metastasis, CRPC progression, M0 management, M1 management and sequencing therapy, and the monitoring of treatment. The conclusions were used to generate a document intended to standardise CRPC patient management and to facilitate decision-making in this stage across Spain.

Materials and methods

The consultation process followed a modified Delphi method. In the first phase, a scientific committee with 4 radiation oncologists plus a coordinator (supplementary data) identified several critical controversial areas in CRPC and developed a questionnaire covering 7 topics with a total of 116 questions. In the second phase, URONCOR sent the questionnaire to a working panel of 25 experts (supplementary data) to obtain their opinions on best practice. The questions were answered in two separate rounds and a face-to-face meeting, where panelists were able to discuss their answers and to vote again on any conflicting items through an anonymous televoting system (9–10 February 2017, Madrid, Spain).

Questions that resulted in an absolute consensus (100%) were classified as having unanimity, 80% or more was classified as a strong consensus, 70–79% represented a moderate consensus and 29–69% was defined as having no consensus. Issues that reached a moderate consensus or had no consensus in the second round were debated in the face-to-face meeting.

Results

The questionnaire covered a total of 116 clinically relevant issues categorised under 7 controversial areas relating to CRPC and its treatment: CRPC definition, (Topic 1), Symptomatic patients (Topic 2), Diagnosis of metastasis (Topic 3), CRPC progression (Topic 4), M0 management (Topic 5), M1 management and sequencing therapy (including metastasis monitoring; Topic 6) and Monitoring of response (Topic 7).

After the two rounds and the face-to-face meeting, a consensus was reached on 108 of the 116 questions (93%), with unanimity on 22 items (19.0%) and a strong consensus on 86 questions (74.1%). Three questions (2.6%) reached a moderate consensus while the remaining five questions had no consensus (4.3%) (Figs. 1 and 2, Table 1).

Table 2 shows the voting results of the expert panel obtained by the Urological Tumours Working Group (URONCOR) of the Spanish Society of Radiation Oncology (SEOR).

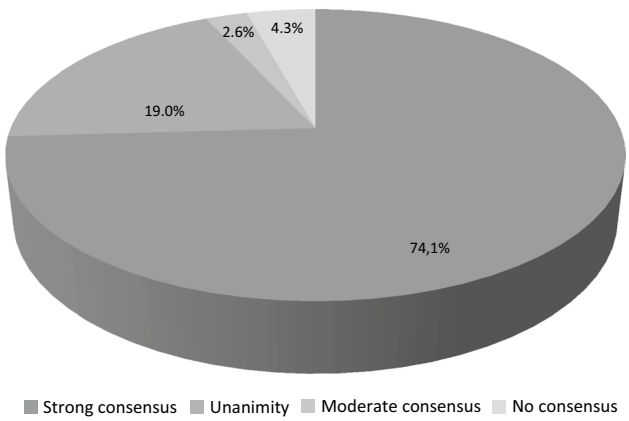

Fig. 1 Consensus after the face-to-face session (percentage)

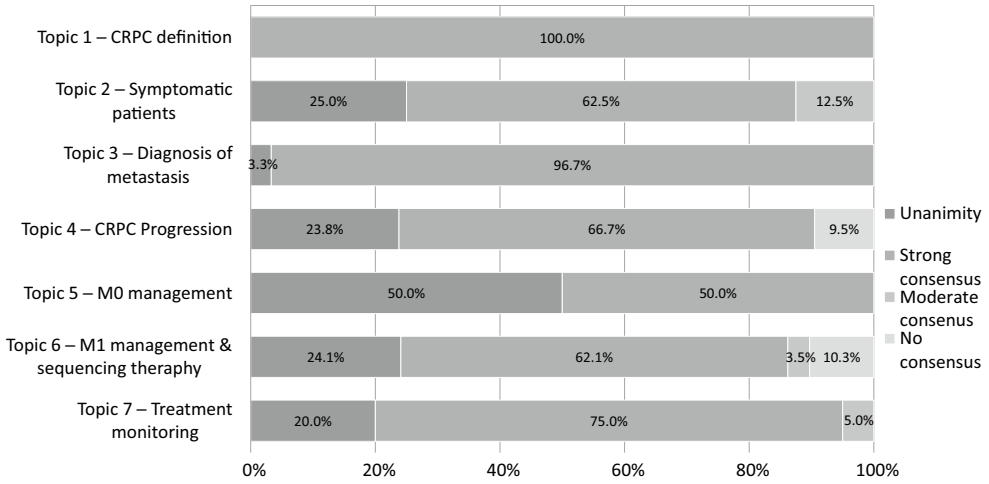

Fig. 2 Results by topic (percentage) of the consensus after the face-to-face session

Table 1 Results of the consensus reached after the face-to-face session by topic (number of questions, percentage)

	N	Unanimity *N* (%)	Strong consensus *N* (%)	Consensus *N* (%)	No Consensus *N* (%)
Topic 1—CRPC definition	2		100.0%		
Topic 2—Symptomatic patients	8	25.0%	62.5%	12.5%	
Topic 3—Diagnosis of metastasis	30	3.3%	96.7%		
Topic 4—CRPC progression	21	23.8%	66.7%		9.5%
Topic 5—M0 management	6	50.0%	50.0%		
Topic 6—M1 management and sequencing therapy	29	24.1%	62.1%	3.5%	10.3%
Topic 7—Treatment monitoring	20	20.0%	75.0%	5.0%	
	116	22 (19%)	86 (74.1%)	3 (2.6%)	5 (4.3%)

Consensus development and panel discussion

Topic 1—CRPC definition

Several definitions of CRPC have been proposed over time. Similarly, the diagnostic criteria used in clinical studies have been extremely heterogeneous [6]. Recently, the European Expert Consensus Panel [15] defined CRPC patients as men with castrate serum testosterone levels and confirmed PSA progression. Spanish urologist experts added radiological progression to the definition of CRPC [16]. The St Gallen expert group considered that a confirmed rising PSA is sufficient to diagnose CRPC in patients on ADT with castrate levels of testosterone [17].

The panel strongly agreed (96%) that CRPC was defined by a documented rising PSA ($\geq$2 ng/ml) and/or radiological progression in men with testosterone levels of $<$50 ng/dl ($<$1.7 nmol/l). In addition, they strongly agreed (88%) that a rising PSA after the use of 2 or more hormonal therapies was not required to define CRPC.

Topic 2—Symptomatic patients

In the TAX327 trial, pain response was found to be a prognostic end-point for overall survival, even if it did not meet strict surrogacy criteria [18]. There is a degree of uncertainty among the end-point criteria on whether to consider an asymptomatic/minimally symptomatic patient in clinical trials [11, 19]. The URONCOR consensus statement agreed to define these patients as those with bone metastasis without pain or mild/moderate pain controlled with first- or second-line WHO pain scale analgesics [20], or patients who have shown a good analgesic response to palliative RT and/or to bisphosphonates [21]. In addition, different publications support the use of symptom assessment tools to evaluate pain in CRPC [22–24].

The panel agreed that a minimally symptomatic CRPC patient was defined as having a low score in validated pain scales (100%) and showing a response to non-steroidal anti-inflammatory drugs (NSAID) (100%). A strong consensus was reached on previous response to antialgic radiotherapy (80%) whereas opioid response was considered irrelevant

Table 2 Consensus panel voting results on CRPC from the Urological Tumour Working Group (URONCOR) of the Spanish Society of Radiation Oncology

	Yes	No	Consensus level
Topic 1—CRPC definition			
In patients with castrate levels of testosterone, CRPC can be defined as:			
Confirmed PSA progression (> 2 ng/ml) and/or radiological progression	**96%**	4%	SC
Confirmed PSA progression (> 2 ng/ml) and/or radiological progression after ≥ 2 prior hormonal therapies	12%	**88%**	SC
Topic 2—Symptomatic patients			
Criteria to define a minimally symptomatic patient			
Low score on validated pain scales	**100%**	0%	U
Pain response to NSAID/paracetamol	**100%**	0%	U
Pain control by opioids	12%	**88%**	SC
Previous response to antalgic radiotherapy	**80%**	20%	SC
Scales used to assess the patient's pain:			
BPI–SF (Brief Pain Inventory – Short Form)	**92%**	8%	SC
Visual analogic scale	**96%**	4%	SC
Subjective patient assessment/verbal scales	28%	**72%**	MC
Scales are not important in evaluating patient pain	4%	**96%**	SC
Topic 3—Diagnosis of metastasis			
Bone scan (BS)			
In a CPRC patient, a BS would be appropriate to perform in the following scenarios:			
At CRPC diagnosis, regardless of PSA levels	**88%**	12%	SC
When PSA level is > 10 ng/ml and/or PSA-DT at < 6 months	**92%**	8%	SC
At the onset of bone pain	**92%**	8%	SC
Given a negative BS in an asymptomatic M0 CRPC patient, the test would be repeated under the following circumstances:			
PSA level of > 10 ng/ml and/or PSA-DT at < 6 months	**92%**	8%	SC
PSA level of > 2 ng/ml and/or PSA-DT at 6–12 months	16%	**84%**	SC
Every 3–6 months regardless of PSA values	**20%**	**80%**	SC
Exclusively with the onset of pain	16%	**84%**	SC
In a CPRC patient with bone pain, in the event of a negative/inconsistent BS:			
Wait to know what the PSA kinetics are	12%	**88%**	SC
An additional imaging test is required (standard x-rays of areas of concern, axial skeleton MRI scan, CT bone scan or choline PET/CT)	**92%**	8%	SC
CT Scan			
In a CPRC patient, a chest, abdomen and pelvis CT scan would be appropriate to perform:			
At CRPC diagnosis, regardless of PSA levels	**96%**	4%	SC
With a PSA level of > 10 ng/ml and/or PSA-DT at < 6 months	**88%**	12%	SC
At the onset of metastatic related symptoms	**96%**	4%	SC
In a CPRC M0 asymptomatic patient, with a negative CT scan, the following test should be repeated:			
With a PSA level of > 10 ng/ml and/or PSA-DT at < 6 months	**96%**	4%	SC
With a PSA level of > 2 ng/ml and/or PSA-DT at 6–12 months	16%	**84%**	SC
Every 3–6 months regardless of PSA values	16%	**84%**	SC
Only if they present symptoms	16%	**84%**	SC
In a symptomatic CPRC patient, in the event of a negative/inconsistent CT Scan:			
Wait to know what the PSA kinetics are	12%	**88%**	SC
An additional imaging test is required (whole-body MRI or choline PET/CT)	**100%**	0%	U
Choline PET/CT/Whole-body MRI			
Performing PET/CT would be appropriate for CRPC patients:			
In order to confirm inconclusive M1 test results	**88%**	12%	SC
Following a negative conventional cancer staging study (CT and BS)	12%	**88%**	SC

Table 2 (continued)

	Yes	No	Consensus level
Following a negative conventional cancer staging study (CT and BS) and aggressive PSA kinetics	**96%**	4%	SC
Performing a whole-body MRI would be the best option for CRPC patients:			
In order to confirm inconclusive M1 test results	**100%**	0%	U
Following a negative conventional cancer staging study (CT and BS)	20%	**80%**	SC
Following a negative conventional cancer staging study (CT and BS) and aggressive PSA kinetics	**80%**	20%	SC
Oligometastatic CPRC patient			
Definition criteria:			
Lack of visceral disease	8%	**92%**	SC
Ganglionic and/or bone disease (5 areas or fewer)	**92%**	8%	SC
Images needed in order to diagnose the oligometastatic CPRC patient:			
CT and BS	**84%**	16%	SC
Choline PET/CT	**88%**	12%	SC
Whole-body MRI	**80%**	20%	SC
Do you agree with the following statement?			
Choline PET/TC is not useful to identify oligometastasis in patients with a low PSA level ($\leq$ 1 ng/ml)	**96%**	4%	SC
Topic 4—CRPC progression			
Do you agree that the following statements define the progression of a CPRC patient?			
Exclusive biochemical progression	12%	**88%**	SC
Radiological progression	**96%**	4%	SC
Clinical progression (pain, overall status)	**88%**	12%	SC
Which statements define primary resistance to therapies targeting the androgen receptor pathway (enzalutamide/abiraterone):			
Absence of decline in PSA level ($\geq$ 30%) during the first 3 months	12%	**88%**	SC
Sustained PSA progression within 3–4 months of therapy initiation	68%	32%	NC
Radiological progression within 3–4 months of therapy initiation	**92%**	8%	SC
Statements related to the flare-up occurrence			
A flare-up is defined as a temporary clinical and/or biochemical worsening since therapy initiation	**92%**	8%	SC
A flare-up occurs with taxane treatment	**100%**	0%	U
A flare-up occurs with enzalutamide treatment	56%	44%	NC
A flare-up occurs with abiraterone treatment	**100%**	0%	U
The following parameters are predictive factors of poor response to therapies:			
High primary tumour Gleason score	**100%**	0%	U
Short response duration after first-line hormonal therapy (LHRH)	**96%**	4%	SC
Presence of visceral metastasis	**100%**	0%	U
Short PSA-DT	96%	4%	SC
High LDH and/or alkaline phosphatase	**92%**	8%	SC
Moderate to severe pain score	**92%**	8%	SC
Overall poor condition (ECOG performance status)	**100%**	0%	U
The following parameters are prognostic factors of disease progression:			
Presence of circulating tumour cells ($\geq$ 5/7.5 ml)	**84%**	16%	SC
Presence of androgen receptor splice variant (AR-V7)	**92%**	8%	SC
Do you agree with the following definition of the biochemical progression of the CPRC patient?			
Three consecutive PSA increases one week apart, resulting in two 50% increases over the nadir and a PSA level of > 2 ng/ml	**88%**	12%	SC
Three consecutive PSA increases one week apart, resulting in two 50% increases over the nadir and a PSA level of > 1 ng/ml	12%	**88%**	SC

Table 2 (continued)

	Yes	No	Consensus level
Topic 5—M0 management			
In an M0 CRPC patient, do you agree with the following statements?			
An initial BS should be requested for PSA levels of > 2 ng/ml	**84%**	16%	SC
For PSA levels of > 2 ng/ml and negative BS, the test should be repeated when PSA levels reach ≥ 5 ng/ml	**88%**	12%	SC
For PSA levels of ≥ 5 ng/ml and negative BS, the test should be repeated each time the PSA level doubles and PSA should be tested every 3 months	**88%**	12%	SC
In an M0 CRPC patient with local clinical progression, the first-line therapy would be:			
Radiotherapy (if no prior RT) or salvage surgery	**100%**	0%	U
Docetaxel	0%	**100%**	U
New antiandrogen therapies (enzalutamide/abiraterone)	0%	**100%**	U
Topic 6—M1 management and sequencing therapy			
In an asymptomatic/minimally symptomatic M1 CRPC patient the first-line therapy would be:			
Enzalutamide/abiraterone in most cases	**100%**	0%	**U**
Docetaxel in most cases	0%	**100%**	**U**
Docetaxel in some aggressive cases	**92%**	8%	**SC**
In an initially asymptomatic or minimally symptomatic M1 CRPC patient, the following factors would influence the choice of treatment:			
Visceral metastases	**96%**	4%	**SC**
Hypertension	44%	56%	**NC**
History of cardiovascular disease	**72%**	28%	**MC**
History of seizures	**80%**	20%	**SC**
Contradindications for steroid use	**96%**	4%	**SC**
In an asymptomatic/minimally symptomatic M1 CRPC patient with visceral metastasis, first-line therapy would be:			
Enzalutamide	**80%**	20%	SC
Abiraterone	0%	**100%**	U
Docetaxel	20%	**80%**	SC
In an asymptomatic/minimally symptomatic M1 CRPC patient, secondary hormonal manipulations			
Are suitable for patients who are not candidates for chemotherapy only when enzalutamide/abiraterone are not available	**88%**	12%	SC
Are suitable for patients who are not candidates for chemotherapy regardless of enzalutamide/abiraterone availability	0%	**100%**	U
Are suitable for all patients, regardless of whether they are chemotherapy candidates or not	4%	**96%**	SC
If there is progression…			
A biopsy of the metastatic lesion would be performed to check for a change in the tumour phenotype.	52%	48%	NC
In a symptomatic M1 CRPC patient the first-line therapy would be:			
New antiandrogenic drugs (enzalutamide/abiraterone)	16%	**84%**	SC
Docetaxel	**84%**	16%	SC
Radium-223 (in bone/non-visceral metastases)	**92%**	8%	SC
Do you agree with the following statement?			
Most CPRC with symptomatic bone metastases should be treated with bone-targeting therapies (bisphosphonate, denosumab, if there areno contraindications).	**88%**	12%	SC
If you answered yes to the previous question, the bone-targeting therapies must be continued:			
For 12–24 months	55%	45%	NC
Until the onset of bone progression	**82%**	18%	SC
The local control of oligometastasis…			
Decreases symptoms.	**92%**	8%	SC
Delays the start of a new systemic treatment	**88%**	12%	SC
Increases overall/progression-free survival	**84%**	16%	SC

Table 2 (continued)

	Yes	No		Consensus level
In oligometastatic CPRC patients…				
Local ablative therapy in addition to the new antiandrogenic drugs (enzalutamide/abiraterone) must be considered	**92%**	8%		SC
A radical prostate treatment should be performed	**100%**	0%		U
In the CPRC patient the following supportive therapies must be offered:				
Calcium and vitamin D when denosumab or bisphosphonates are prescribed	**96%**	4%		SC
External radiotherapy, radiopharmaceuticals and analgesia in cases of painful bone metastases	**100%**	0%		U
Corticosteroids and surgical evaluation and radiation in patients with spinal cord compression	**100%**	0%		U
Topic 7—Treatment monitoring				
Imaging test suitable to evaluate bone metastasis response to the therapy				
Tc-99 m bone scan	**84%**	16%		SC
Whole body MRI and/or axial skeleton	**92%**	8%		SC
Choline PET/TC	**84%**	16%		SC
In an asymptomatic/minimally symptomatic CPRC patient, does the first-line therapy choice influence the frequency of patient monitoring in the following?				
Follow-up patient visits	**100%**	0%		U
Imaging tests frequency	4%	**96%**		SC
Analytic testing	**84%**	16%		SC
Additional blood pressure monitoring	**80%**	20%		SC
If you answered yes, which is your preferred choice of action during the first 3 months of enzalutamide therapy:				
	1/2 weeks	Monthly	Quarterly	
Frequent follow-up visits	4%	**80%**	16%	SC
Imaging tests frequency	14%	**84%**	12%	SC
Analytic testing	10%	**70%**	20%	MC
If you answered yes, which is your preferred choice of action during the first 3 months of abiraterone therapy:				
	1/2 weeks	Monthly	Quarterly	
Frequent follow-up visits	**92%**	8%	0%	SC
Analytic testing	**84%**	16%	0%	SC
Additional blood pressure monitoring	**85%**	15%	0%	SC
In an asymptomatic/minimally symptomatic M1 CPRC patient, follow-up tests must be performed:				
Every 3–6 months, regardless of PSA values	**88%**	12%		**SC**
When the PSA values double	**96%**	4%		**SC**
In the event of symptoms related to the metastatic disease appearing	**100%**	0%		**U**
In a symptomatic M1 CPRC patient, follow-up tests must be performed:				
Every 3 months, regardless of PSA values	**84%**	16%		**SC**
Every 6 months, regardless of PSA values	4%	**96%**		**SC**
When the PSA values double	**96%**	4%		**SC**
In the event of new symptoms appearing	**100%**	0%		**U**

Values in bold indicate the consensus

U unanimity, *SC* strong consensus, *MC* moderate consensus, *NC* no consensus, *CRPC* castration-resistant prostate cancer, *PSA* prostate-specific antigen, *NSAID* non-steroidal anti-inflammatory drugs, *BPI-SF* short form of the Brief Pain Inventory questionnaire, *PSA-DT* prostate-specific antigen doubling-time, *MRI* magnetic resonance imaging, *BS* bone Scan, *PET/CT* positron emission tomography/computed tomography, *LHRH* luteinizing hormone-releasing hormone, *LDH* lactate dehydrogenase, *AR* androgen receptor, *RT* radiotherapy

in the definition of CRPC (88%). The panel also strongly agreed that the BPI-SF (Brief Pain Inventory-Short Form) (92%) and a visual analogic scale (96%) should be used to assess patient pain.

Topic 3—Diagnosis of metastasis

There is no agreed definition on what constitutes the standard of care for detection of metastatic disease in CRPC. The EAU-ESTRO-SIOG guidelines [25] stated that in men with

no detectable clinical metastases, baseline PSA level and PSA velocity/PSA doubling-time (DT) have been associated with the time to first bone metastasis, bone metastasis-free survival and overall survival [26, 27].

The RADAR group consensus [28] suggested that in asymptomatic men, a bone scan should be undertaken if PSA levels reached 2 ng/ml and, if negative, to undertake another bone scan if PSA reaches 5 ng/ml and every doubling of PSA level thereafter, based on PSA testing every 3 months.

The Prostate Cancer Working Group PCWG3 [22] recommends that imaging should include cross-sectional imaging (chest, abdomen, pelvis), plus bone scintigraphy.

The emerging role of the next-generation imaging methods seems promising, despite a lack of systematically conducted prospective studies. The prostate-specific membrane antigen (PSMA) PET can be considered as a highly promising tool in prostate cancer imaging due to higher detection rates, as compared with ^{11}C-choline PET for lymph nodes as well as bone lesions, especially at low PSA levels [29]. Significantly, imaging strategies restricted to known sites of disease risk could miss disease progression at new sites. The NCCN (National Comprehensive Cancer Network) [30] includes MRI and PET.

The panel strongly agreed that a bone scan (BS) should be requested at CRPC diagnosis, regardless of PSA level (agreement of 88%), with a PSA level of > 10 ng/ml and/or PSA-DT at < 6 months (agreement of 92%) and at the onset of bone pain (92%).

Similarly, it was strongly agreed that a CT scan should be performed at diagnosis, regardless of PSA levels (96%), with a PSA level of > 10 ng/ml and/or PSA-DT < 6 months (88%) and at the onset of metastatic related symptoms (96%).

With regard to the use of choline PET/CT and whole-body MRI, there was a strong consensus that both tests were appropriate as a follow-up to inconclusive M1 test results (Choline PET/CT, 88%; whole-body MRI, unanimity). The panel also strongly agreed that choline PET/CT (96%) should be also performed in the event of a negative conventional extension study (CT and BS) and aggressive PSA kinetics. Likewise, there was a strong consensus on whole-body MRI (80%) being performed in this situation.

The definition of oligometastasis has evolved over time. Originally defined as five or less metastatic sites [31], it has been proposed as a clinically significant state separate from the polymetastatic disease [32], with a better prognosis and survival rates compared with patients with extensive metastatic disease [31, 32]. Significantly, aggressive local therapy [33] during this time could delay the need for systemic therapies and/or prolong progression-free survival. Recent data show that in men with PSA-recurrent prostate cancer, a prolonged metastasis-free survival is significantly associated with a longer overall survival [34]. The St Gallen consensus 2017 debated whether to propose a new clinical entity, the oligo-progressive mCRPC, but no agreement was reached on this issue [35].

The panel reached a strong consensus that the oligometastatic CRPC patient is defined as having lymph node and/or bone disease (5 or fewer sites) (92%). There was also a strong consensus that CT and BS (84%), choline PET/CT (88%) and whole-body MRI (80%) should be used as diagnostic tools for these patients. Finally, there was a strong consensus (96%) that choline PET/TC is not useful to identify oligometastasis in patients with a low PSA level (≤ 1 ng/ml).

Topic 4—CRPC progression

The definition of CRPC progression is another cause for controversy and has varied over time. In many studies it has been considered as a rise in PSA levels following castration [3]. However, PSA alone is not reliable enough for monitoring disease activity in advanced CRPC because visceral metastases may develop in men without rising PSA [36]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements, and clinical benefit in assessing men with CRPC. The PGW3 panel [22] and St. Gallen 2015 [17] stressed that agents with a proven overall survival benefit should not be stopped due to PSA progression alone. Moreover, at least two of three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled before stopping treatment.

In addition, the European expert panel consensus [15] defines primary resistance to AR pathway-targeted agents as a radiological progression within 3 months following therapy initiation, while a limited decrease in PSA level or progression within 3 months of therapy initiation was not sufficient for the diagnosis.

While short response to initial hormonal therapy seems to be associated with poor response to subsequent hormonal therapies, this is not always an indicator of absolute androgen independence and does not exclude any potential benefit from novel AR-targeting strategies [15], such as abiraterone or enzalutamide, which have demonstrated a positive outcome in overall survival and improvement in quality of life [7, 9].

There was a strong consensus that radiological (96%) and clinical progression (pain, overall status) (88%) had to be present in order to define disease progression. In contrast, the panel voted against an exclusive biochemical progression criteria in the definition (88%).

In addition, the experts strongly agreed that primary resistance to enzalutamide/abiraterone is defined as radiological progression within 3–4 months of therapy initiation (92%), while an abscense of decline in PSA level (≥ 30%)

within 3 months does not serve to identify primary resistance (88%). There was no consensus on whether sustained PSA progression within 3–4 months of therapy initiation must be present in order to define resistance to these therapies.

Even though there is no complete agreement on a precise definition of a flare occurrence, there is a broad consensus that it is characterised by a rise in the PSA level, followed by a decline below baseline values after initiating different therapies [37, 38]. A bone scan flare has been also described by the NCCN [39] and must be clearly differentiated from "disease progression". The PCWG3 suggests the use of the 2 + 2 rule to distinguish flare from true progression in patients with osseous disease at baseline.

A transient rise in PSA levels at therapy initiation has been described in patients receiving taxanes and abiraterone [15, 39]. In a phase II study in mCRPC treated with abiraterone [39], bone scan flare was observed in a large proportion of patients (30% of the total and 44% of those who experienced a ≥ 50% decline in PSA), suggesting that more investigation is needed to clarify the potentially confounding effect of the bone scan flare phenomena. This flare phenomenon precedes actual response to treatment and can be misinterpreted as therapeutic failure, leading to premature discontinuation of potentially effective agents. While different studies have shown a flare occurrence after abiraterone treatment [35, 40, 41], no such phenomena have been observed with enzalutamide [42].

The panel reached a strong consensus that a flare is defined as a temporary clinical and/or biochemical worsening of therapy initiation (92%). They unanimously agreed that flares occur following taxane and abiraterone treatment. There was no consensus on the possible flare effect of enzalutamide.

Topic 5—M0 management

There is a lack of information in current clinical practice guidelines on which imaging modality should be used for M0 patients. It is crucial to consider the potential impact on survival in an early identification of asymptomatic M1. The ENTHUSE M0 trial found a high frequency of asymptomatic metastasis (32%) in patients thought to have M0 CRPC, highlighting the urgent need to improve imaging strategies for metastatic disease [43, 44]. Recommendations on when to initiate and repeat imaging in M0 CRPC patients have been published by the RADAR group [28].

The panel voted on the M0 definition criteria proposed by the RADAR group and they strongly agreed that in an M0 CRPC a baseline bone scan is required for a PSA level of ≥ 2 ng/ml (84%). The experts reached a strong consensus that a repeat bone scan should be performed if the PSA level rises to 5 ng/ml after the negative initial bone scan (88%). They also strongly agreed that for PSA levels of ≥ 5 ng/ml and a negative bone scan, the test should be repeated every doubling of PSA level thereafter based on PSA testing every 3 months (88%).

The St Gallen 2015 [17] recommendation for men with M0 CRPC was to continue with ADT and add the older endocrine manipulations without proven survival benefit while acknowledging the lack of evidence about the benefits of abiraterone or enzalutamide, while different studies support the use of palliative radiotherapy in this clinical situation.

The panel unanimously agreed that first-line treatment in an M0 CRPC patient with local clinical progression was radiotherapy (if there had been no previous radiotherapy) or salvage surgery. They also unanimously agreed that docetaxel, abiraterone or enzalutamide should not be administered in these cases until evidence from the ongoing randomized clinical trials becomes available.

Even though the results on the benefits of the new antiandrogens were not known when the different phases of the consensus were underway, the results of two phase III studies have confirmed the benefits of enzalutamide (PROSPER) and apalutamide (SPARTAN) in M0 CRPC patients and PSA doubling time < 10 months [45, 46]. Both drugs have constistently improved progression free survival compared with placebo, as well as metastasis free survival.

Topic 6—M1 management and sequencing therapy

Asymptomatic/minimally symptomatic M1 CRPC patient More than 84% of patients have metastases at CRPC diagnosis. In those without metastases at diagnosis, 33% of patients with CRPC develop metastases within 2 years of their diagnosis [6, 7, 47]. The new androgen-receptor inhibitors which demonstrates efficacy in the metastatic CRPC setting have changed the paradigm of CRPC treatment [28]. Abiraterone and enzalutamide have been evaluated as first-line agents in asymptomatic patients [48, 49] and are recommended as first-line therapy in the ESMO [50] and SEOM [3] Clinical Practice Guidelines.

The St Gallen consensus (2015, 2017) [17, 35] agreed that asymptomatic men with mCRPC should receive abiraterone or enzalutamide as first-line treatment, independently of whether they had received ADT alone or ADT plus docetaxel in the castration-naïve setting [16, 34]. Similarly, the EAU-ESTRO-SIOG guidelines [25] proposed different therapies, including abiraterone, enzalutamide, sipuleucel-T and docetaxel, and the URONCOR consensus statement includes sipuleucel-T and abiraterone acetate plus prednisone [21].

Visceral metastases are nowadays more commonly detected [36] and autopsy studies on men who died from prostate cancer suggested a higher prevalence of visceral metastases in up to 66% of selected cases [51]. Even though this population has a poor prognosis and are frequently

excluded from other trials, research with new survival-prolonging treatments has changed this paradigm. In the PREVAIL study, enzalutamide treatment showed a consistent benefit in some patients with visceral metastatic disease [52].

The panel unanimously voted that most asymptomatic/minimally symptomatic M1 CRPC patients should receive abiraterone or enzalutamide as first-line treatment while docetaxel should only be used in some aggressive cases. They unanimously voted not to use docetaxel as a first option in many cases.

In an asymptomatic/minimally symptomatic M1 CRPC patient with visceral metastases, the panel strongly agreed (80%) to consider enzalutamide as first-line treatment. They voted unanimously not to consider abiraterone as first-line treatment and reached a strong consensus on not recommending docetaxel as first-line therapy (80%).

In accordance with the results of COU-32 [53] and PREVAIL [52], the NCCN [30] considers that enzalutamide treatment should be monitored for fatigue, diarrhoea, hot flashes and seizures (reported in 0.9% of men on enzalutamide). The side effects of abiraterone require monitoring for hypertension, hypokalaemia, peripheral oedema, atrial fibrillation, congestive heart failure, liver injury and fatigue.

The panel strongly agreed that the choice of treatment for these patients would be influenced by the following factors: visceral metastases (96%), cardiovascular history (72%), prior seizures (80%) and steroid contraindications (96%). Only half of them considered that hypertension would have an influence on their decision.

Finally, there was a strong consensus (88%) that secondary hormonal manipulations are suitable for patients who are not candidates for chemotherapy, regardless of enzalutamide or abiraterone availability.

Symptomatic M1 CRPC patient The EAU-ESTRO-SIOG guidelines [25] suggest that symptomatic M1 CRPC patients should receive docetaxel as first-line therapy and radium-223 if they have bone/non-visceral metastasis. The second-line choice would include enzalutamide, abiraterone, docetaxel, cabazitaxel or radium-223, depending on previous therapy. The SEOM guidelines [3] also suggest that abiraterone or enzalutamide are an alternative first-line treatment for symptomatic mCRPC patients who are docetaxel-naïve or unfit or unwilling to receive docetaxel.

The panel strong agreed that the first-line therapy for symptomatic M1 CRPC should be docetaxel (84%) and radium-223 in patients with bone metastases (non-visceral) (92%), but they did not consider that enzalutamide/abiraterone should be recommended (84%).

There was a strong consensus that most CRPC patients with symptomatic bone metastasis should receive bone-targeting therapies (bisphosphonates, denosumab) (88%) until the onset of the bone progression (82%).

Oligometastatic M1 CRPC patient Interest has increased in the potential role of definitive metastasis-directed therapy for men with oligometastatic disease, defined as few (often ≤ 5) metastatic lesions, even in the absence of symptoms [33]. It has been proposed as a distinct clinical entity from metastasis, considered to be an intermediate state of tumour spread with limited metastatic capacity [32, 33].

In CRPC patients, the management of men with oligometastatic disease is another area where trial data is lacking, making it an important research question [35].

The panel strongly agreed that local control of oligometastasis decreases symptoms (92%), delays the start of a new systemic therapy (88%) and could increase overall survival and/or progression-free survival (84%).

In the CPRC oligometastatic patient, local ablative therapy in addition to enzalutamide/abiraterone must be considered (92%) and it was unanimously agreed that a radical prostate treatment should be also considered.

Topic 7—treatment monitoring

Even though it is generally accepted that regular treatment response monitoring should be undertaken, there are no agreed guidelines on the precise clinical, laboratory and imaging evaluations or on the frequency of scheduling follow-up visits.

According to the EAU-ESTRO-SIOG guidelines, monitoring M1 CPRC treatment should include a physical examination, baseline blood tests, a whole-body CT scan and a bone scan every 6 months.

The NCCN [30] recommend that in M1 patients there must be a physical examination and PSA levels tested every 3–6 months, with a bone scan taken every 6–12 months.

According to the PCWG3 [22], analytical tests should be performed every 3–4 weeks and image tests taken at 8- or 9-week-intervals in case there is a flare occurrence. The URONCOR consensus [21] recommended that patient should be monitored 1 month after initiation therapy and that radiological imaging should be done every 3 months.

Finally, the European consensus of 2014 [14] recommends early imaging at 3 months to detect any resistance to new agents.

There was a strong consensus that a Tc-99 m bone scan (84%), a whole-body MRI and/or axial skeleton (92%), and a Choline PET/TC (84%) were all suitable to evaluate bone metastasis response to the therapy.

The panel unanimously agreed (100%) that in asymptomatic/minimally symptomatic men with M1 CRPC, the choice of first-line therapy influences the frequency of follow-up patient visits, blood tests (84%) and blood pressure

monitoring (80%). Conversely, they strongly agreed that the frequency of imaging tests was not influenced by the first-line therapy choice (96%).

The panel also strongly agreed that during the first 3 months of enzalutamide therapy the frequency of patient visits (80%), blood tests (84%) and blood pressure monitoring (70%) should be done every month.

During the first 3 months of abiraterone therapy, there was also a strong consensus that the frequency of patient visits (80%), blood tests (84%) and additional blood pressure monitoring (70%) should be undertaken every 1–2 weeks.

In an asymptomatic/minimally symptomatic M1 CPRC patient, the panel strongly agreed that follow-up tests must be scheduled either every 3-6 months regardless of PSA values (88%) or, when PSA levels double (96%), and they unanimously agreed that follow-up tests should be performed if symptoms related to the metastatic disease appeared (100%).

In an M1 CPRC symptomatic patient, the panel strongly agreed that follow-up tests must be scheduled either every 3 months regardless of PSA values (84%) or when PSA levels double (96%). They unanimously agreed that follow-up tests should be performed if new symptoms appeared (100%) but they strongly agreed that 6 months was too infrequent, regardless of PSA values (96%).

Conclusion

The present consensus document is intended to be a useful tool, providing radiation oncology specialists with expert guidance on and standards for CRPC patient management in Spain. It provides 116 statements that have been agreed following a modified Delphi method. A strong consensus or unanimity has been reached on 108 out of the 116 (93%) questions. This is especially important considering that CRPC management is still challenging due to the heterogeneity of the disease, the high number of different therapeutic options available, the lack of head-to-head clinical trials, primary or acquired resistance, and the incidence of metastatic progression. In addition to these guidelines the clinical judgement and experience of the treating physician in clinical practice is also required in the decision-making process for each of the different clinically relevant areas for CRPC patients.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest in this article.

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