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# Management of Patients with Advanced Prostate Cancer. Part I: Intermediate-/High-risk and Locally Advanced Disease, Biochemical Relapse, and Side Effects of Hormonal Treatment: Report of the Advanced Prostate Cancer Consensus Conference 2022

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## Abstract

***Background:*** Innovations in imaging and molecular characterisation and the evolution of new therapies have improved outcomes in advanced prostate cancer. Nonetheless, we continue to lack high-level evidence on a variety of clinical topics that greatly impact daily practice. To supplement evidence-based guidelines, the 2022 Advanced Prostate Cancer Consensus Conference (APCCC 2022) surveyed experts about key dilemmas in clinical management.

***Objective:*** To present consensus voting results for select questions from APCCC 2022.

***Design, setting, and participants:*** Before the conference, a panel of 117 international prostate cancer experts used a modified Delphi process to develop 198 multiple-choice consensus questions on (1) intermediate- and high-risk and locally advanced prostate cancer, (2) biochemical recurrence after local treatment, (3) side effects from hormonal therapies, (4) metastatic hormone-sensitive prostate cancer, (5) non-metastatic castration-resistant prostate cancer, (6) metastatic castration-resistant prostate cancer, and (7) oligometastatic and oligoprogressive prostate cancer. Before the conference, these questions were administered via a web-based survey to the 105 physician panel members ("panellists") who directly engage in prostate cancer treatment decision-making. Herein, we present results for the 82 questions on topics 1–3.

***Outcome measurements and statistical analysis:*** Consensus was defined as ≥75% agreement, with strong consensus defined as ≥90% agreement.

***Results and limitations:*** The voting results reveal varying degrees of consensus, as is discussed in this article and shown in the detailed results in the Supplementary material. The findings reflect the opinions of an international panel of experts and did not incorporate a formal literature review and meta-analysis.

***Conclusions:*** These voting results by a panel of international experts in advanced prostate cancer can help physicians and patients navigate controversial areas of clinical management for which high-level evidence is scant or conflicting. The findings can also help funders and policymakers prioritise areas for future research. Diagnostic and treatment decisions should always be individualised based on patient and cancer characteristics (disease extent and location, treatment history, comorbidities, and patient preferences) and should incorporate current and emerging clinical evidence, therapeutic guidelines, and logistic and economic factors. Enrolment in clinical trials is always strongly encouraged. Importantly, APCCC 2022 once again identified important gaps (areas of nonconsensus) that merit evaluation in specifically designed trials.

***Patient summary:*** The Advanced Prostate Cancer Consensus Conference (APCCC) provides a forum to discuss and debate current diagnostic and treatment options for patients with advanced prostate cancer. The conference aims to share the knowledge of international experts in prostate cancer with health care providers and patients worldwide. At each APCCC, a panel of physician experts vote in response to multiple-choice questions about their clinical opinions and approaches to managing advanced prostate cancer. This report presents voting results for the subset of questions pertaining to intermediate- and high-risk and locally advanced prostate cancer, biochemical relapse after definitive treatment, advanced (next-generation) imaging, and management of side effects caused by hormonal therapies. The results provide a practical guide to help clinicians and patients discuss treatment options as part of shared multidisciplinary

decision-making. The findings may be especially useful when there is little or no high-level evidence to guide treatment decisions.



## 1. Introduction

Despite recent progress in the management of advanced prostate cancer, many clinical questions and controversies persist that directly impact daily practice. At the Advanced Prostate Cancer Consensus Conference (APCCC), these topics are discussed in detail, and physician experts then vote in response to a set of predefined multiple-choice questions. The results of the consensus voting can help clinicians and patients engage in shared and multidisciplinary decision-making, especially in situations where high-level evidence is scant or conflicting.

At APCCC 2022, seven areas of clinical controversy in advanced prostate cancer were prioritised for discussion and consensus voting:

1. Intermediate- and high-risk and locally advanced prostate cancer.
2. Prostate-specific antigen (PSA) persistence and biochemical recurrence (BCR) after definitive treatment.
3. Management of side effects caused by hormonal therapy.
4. Management of newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC).
5. Management of nonmetastatic castration-resistant prostate cancer (nmCRPC).
6. Management of metastatic CRPC.
7. Oligometastatic and oligoprogressive prostate cancer.

Before the conference, a multidisciplinary panel of 117 international prostate cancer experts developed 198 multiple-choice consensus questions on these seven topics using the same modified Delphi process that was used at prior APCCCs and has been described previously [1–3]. Most panellists had helped design consensus questions for previous APCCCs. Consensus voting at the APCCCs is performed by panel members who are physician experts and who engage directly in clinical decision-making. In this paper, these voting panel members are referred to as "panellists." At APCCC 2022, of the 105 panellists, 50% were medical oncologists, 29% urologists, and 21% clinical oncologists and radiation oncologists. A total of 43% practiced in Europe, 38% in North America, and 19% in other regions, including Australia, Asia, South America, the Middle East, and Africa (details at www.apccc.org). The 12 nonvoting panel members included 11 experts in nuclear medicine, radiology, pathology, statistics, and health economics, and the patient advocate.

For all questions, unless stated otherwise, panellists were asked to assume that all diagnostic procedures and treatments were readily available including expertise in interpretation and application, that there were no treatment contraindications, and that the patient had no option to enrol in a clinical trial. Unless stated otherwise, consensus questions applied only to fit patients with prostatic adenocarcinoma who had no treatment-limiting comorbidities. Next-generation imaging for prostate cancer was defined as positron emission tomography (PET)-computed tomography (CT)/magnetic resonance imaging (MRI; subsequently referred to as PET/CT, unless stated otherwise) with prostate-specific membrane antigen (PSMA), choline, or fluciclovine tracers and/or whole-body morphological and diffusion-weighted MRI. Panellists were instructed to vote "abstain" if they thought that they lacked expertise on a specific question, had prohibitive conflicts of interest, or should not vote for some other reason. When calculating results, abstainers were excluded from denominators. Similar to 2021, consensus questions were administered via a web-based survey rather than in person due to COVID restrictions.

Levels of consensus were defined a priori as follows: $\geq$75% agreement on an answer option was a consensus and $\geq$90% agreement on an answer option was a strong consensus. In this paper, we present voting results for the 82 consensus questions on topics 1–3. The Supplementary material shows detailed voting results for each question. The 116 questions on topics 4–7 pertain to metastatic disease, oligometastatic/oligoprogressive disease, and nmCRPC, and are reported and published separately.

## 2. Intermediate- and high-risk and locally advanced prostate cancer

For many years, intermediate- and high-risk prostate cancer was staged with conventional imaging based on CT or abdominal/pelvic MRI and bone scan [4–6]. However, next-generation imaging techniques, such as whole-body MRI and PSMA PET have shown higher sensitivity and specificity in this setting [7–14]. Among these techniques, we have particularly robust evidence that PSMA PET is superior to conventional imaging for the detection of metastases [9–14]. In the prospective, randomised, multicentre ProPSMA trial, 302 patients with high-risk prostate cancer underwent PSMA PET or conventional imaging in order to detect metastatic disease [9]. PSMA PET was 27% more accurate (95% confidence interval [CI] 23–31) than CT and bone scan (92% [88–95%] vs 65% [60–69%]; $p < 0.0001$), and in 28% of patients, PSMA PET findings led to a change in management [9]. PSMA PET also produced fewer equivocal results, was associated with less radiation exposure (8.4 vs 19.2 mSv for CT/bone scan), and demonstrated higher inter-reporter agreement. An embedded health economics assessment also demonstrated that a PSMA PET scan was more cost effective than performing conventional imaging for detecting nodal or distal metastases [15]. In another prospective multicentre trial of patients with intermediate- and high-risk prostate

cancer, staging by PSMA PET and conventional imaging identified suspected nodal and bone or visceral metastases in 25% and 6% of patients, respectively, and staging by PSMA PET led to a change in planned management in 23 of 108 patients (21%) [10]. These findings and those from other important studies have led to the regulatory approval of PSMA PET [9–15]. It has been suggested by some experts to refine the tumour-node-metastasis (TNM) staging system by including a notation for PSMA PET–positive lesions not seen on conventional imaging [16]. Some guidelines also now include PSMA PET as an option for staging patients with prostate cancer [5,6]. For those with unfavourable intermediate- or high-risk disease, current National Comprehensive Cancer Network (NCCN) guidelines classify PSMA PET as a first-line staging tool due to its greater sensitivity and specificity than conventional imaging [5]. Current guidelines from the European Association of Urology (EAU) also describe PSMA PET as more accurate than CT and bone scan for staging high-risk disease, but the authors advise physicians to be aware that we still lack data on whether changing treatment due to PSMA PET results ultimately affects patient outcomes [6]. The APCCC 2022 panel discussed questions related to intermediate and high-risk localised prostate cancer (see Table 1 and supplement 1 for details).

**Q1.** A total of 87% of panellists voted for and 14% voted against refining the metastatic classification (N and M) in TNM to include a notation for PSMA PET–positive lesions, that is, as suggested by the PROMISE paper [16]. (Consensus to refine the metastatic classification in TNM.)

**Q2.** For patients with clinically localised high-risk prostate cancer, 77% of panellists voted to recommend PSMA PET and 23% voted not to recommend it. (Consensus for PSMA PET for high-risk disease.)

**Q3.** For patients with clinically localised unfavourable intermediate-risk (NCCN definition) prostate cancer, 52% of panellists voted to recommend PSMA PET and 48% voted not to recommend it. There were two abstentions. (No consensus for any given answer option.)

**Q4.** For patients with clinically localised favourable intermediate-risk (NCCN definition) prostate cancer, 92% of panellists voted not to recommend PSMA PET and 8% voted to recommend it. There were two abstentions. (Strong consensus not to recommend PSMA PET for favourable intermediate-risk disease.)

**Q5.** For systemic staging of clinically localised prostate cancer, in addition to MRI of the prostate, 78% of panellists voted to recommend upfront PSMA PET with or without subsequent conventional imaging, while 22% voted to recommend PSMA PET only after conventional imaging is found to be negative or indeterminate. (Consensus for performing the PSMA PET upfront.)

Although PSMA is predominantly expressed in prostate cancer cells, it is also found in some benign cells (eg, those associated with neurogenic tissue, Paget's disease, thyroid adenomas, granulomatous disease, and adrenal adenomas) and in other types of malignant cells (renal cell carcinomas, lung tumours, glioblastomas, hepatocellular carcinomas, and thyroid cancers), indicating that PSMA, despite its name, is not prostate specific [17,18]. In addition, DNA damage can upregulate PSMA expression in keeping with its function as a folate hydrolase [19,20]. When used as a tracer, 18F-PSMA-1007 can undergo nonspecific accumulation in bone, which could also lead to false-positive results [18]. In addition, studies have reported PSMA ligand uptake in healing bone fractures, degenerative changes, and fibrocartilage lesions [18,21]. Hence, PSMA-targeted imaging, while sensitive for the detection of prostate cancer, is not always specific. To reduce the false-positive rate, it can be helpful to consider the intensity of PSMA uptake and correlative findings in the CT component. However, currently there is no validated method (except biopsy) for determining whether a PSMA-positive bone lesion is a metastasis [5]. In selected situations, skeletal lesions detected on PSMA PET may require further evaluation, such as through MRI or a biopsy [22]. Structured template reporting using a system such as the E-PSMA EANM standardised reporting guidelines enables harmonisation of diagnostic interpretation criteria [23].

**Q6.** For patients with clinically localised prostate cancer with PSMA-positive findings consistent with metastases in the bone on the CT component of upfront PSMA PET, 78% of panellists voted not to recommend additional imaging (eg, MRI or bone scintigraphy) and 22% voted to recommend it. (Consensus not to recommend additional imaging.)

**Q7.** For patients with clinically localised prostate cancer and PSMA PET–positive lesions in the bone without a correlate on the CT component of upfront PSMA PET, 73% of panellists voted to recommend additional imaging (eg, MRI or bone scintigraphy) and 27% voted not to recommend it. (No consensus for any given answer option.)

For detecting bone metastases in prostate cancer, whole-body MRI is reported to be more sensitive and specific than bone scintigraphy [24,25]. The addition of diffusion-weighted imaging to whole-body MRI can detect metastases in lymph nodes and other soft tissues. In one study of 100 patients with high-risk prostate cancer, whole-body MRI with diffusion-weighted imaging outperformed bone scans for the detection of bone metastases, and performed as well as CT for detecting pathological lymph nodes and visceral metastases [26]. More recently, in a prospective single-centre study of 79 patients with high-risk prostate cancer, PSMA PET outperformed other imaging techniques, including whole-body MRI with diffusion-weighted imaging, for the primary staging of distant metastases [27].

**Q8.** For patients with clinically *localised high-risk* prostate cancer, 91% of panellists voted not to recommend whole-body, diffusion-weighted MRI for systemic staging and 9% voted to recommend it. (Strong consensus not to recommend whole-body MRI.)

**Q9.** For patients with clinically *localised intermediate-risk* prostate cancer, 95% of panellists voted not to recommend whole-body, diffusion weighted MRI for systemic staging and 5% voted to recommend it. (Strong consensus not to recommend whole-body MRI.)

Several PSMA ligands are currently available and are primarily radiolabelled with one of two positron-emitting isotopes: gallium-68 ($^{68}$Ga) and fluorine-18 ($^{18}$F) [28–31]. In Europe, initially, $^{68}$Ga-PSMA-11 was the most commonly used PSMA agent, but recently, $^{18}$F-PSMA ligands (eg, $^{18}$F-

DCFPyL or $^{18}$F-PSMA-1007) have become more available and are frequently used instead [28–31]. Logistical superiority is the major differentiator between $^{18}$F PSMA ligands and $^{68}$Ga-PSMA ligand; $^{18}$F-PSMA ligands have a longer half-life (110 vs 68 min for $^{68}$Ga) and higher production yields (currently 100-fold higher), making them more accessible and economical ($^{18}$F is a cyclotron product, while $^{68}$Ga is predominantly generator-based) [28]. Tracers that are approved by the Food and Drug Administration for this purpose include $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL [32].

The tracers $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL, and most other currently available PSMA tracers undergo renal excretion, which can cause a high background signal in the urinary tract. When using these tracers, it is occasionally difficult to differentiate between urine retained in the ureters and ligand uptake in small adjacent pelvic lymph nodes [30]. In contrast, $^{18}$F-PSMA-1007 is primarily excreted by the liver; only 1–2% of the injected $^{18}$F-PSMA-1007 activity is eliminated in urine [33]. In one study, the use of $^{18}$F-PSMA-1007 increased readers' confidence in interpreting PSMA-avid lesions near the ureter, bladder, and urethra as tumour tissue even when scans with other PSMA tracers had produced equivocal results [22]. However, because $^{18}$F-PSMA-1007 exhibited a higher rate of nonspecific focal bone marrow uptake (22%) compared with other PSMA tracers, the authors recommended using MRI to validate bone marrow positivity on $^{18}$F-PSMA-1007 in cases where the CT component was negative. NCCN guidelines recommend that positive PSMA PET results undergo radiographic or histological confirmation when possible [5].

**Q10.** For patients with high-risk prostate cancer for whom radical local treatment (radical prostatectomy [RP] or radiation therapy [RT]) of the primary tumour is planned, and who have one to three bone lesions with intense uptake on upfront $^{68}$Ga-PSMA-11 or $^{18}$F-DCFPyL (piflufolastat) PSMA PET *without* a correlate on the CT component, 63% of panellists voted for correlative conventional imaging (eg, MRI or bone scintigraphy), 24% voted not to perform further investigations of possible metastases, and 13% voted for biopsy if feasible. (No consensus for any given answer option, but a combined 76% voted for additional investigations.)

**Q11.** For patients with high-risk prostate cancer for whom radical local treatment (RP or RT) of the primary tumour is planned, and who have one to three lesions evident in the bone with intense uptake on upfront $^{18}$F-PSMA-1007 PET/CT *without* a correlate on the CT component, 63% of panellists voted for correlative conventional imaging (eg, MRI or bone scintigraphy), 19% voted not to perform further investigations of possible metastases, 14% voted for biopsy if feasible, and 4% voted for additional imaging with $^{68}$Ga-PSMA-11 PET. (No consensus for any given answer option, but a combined 81% voted for additional investigations.)

The routine integration of next-generation imaging techniques, such as PSMA PET, into the primary staging of prostate cancer may increase the diagnosis of de novo synchronous oligometastatic/low-volume disease [34]. However, there is currently no evidence regarding the prognosis or best management of patients whose prostate cancer is diagnosed as metastatic based on PSMA PET–positive lesion(s) but do not have a correlate on conventional scans (CT or bone scintigraphy). Disease upstaging by PSMA PET can deny a patient potentially curative therapy [35,36]. In the absence of prospective studies demonstrating a survival benefit, caution should be exercised about basing treatment decisions on next-generation imaging alone [6,37]. It is not yet clear whether patients with metastases detectable only by PSMA PET should be managed in the same way as patients whose disease is metastatic based on conventional imaging [38]. Conversely, because the false-positive rate with bone scan and CT is higher than that with PSMA PET, the use of PSMA PET can also downstage patients from oligometastatic/low-volume disease to absence of metastases (M0) [9].

Although palliative systemic therapy is the standard of care for metastatic prostate cancer, some patients with prostate cancer having a limited number of metastases that are visible only on next-generation imaging might have a less aggressive disease course and might therefore be treated with local treatment of the primary tumour with or without metastasis-directed therapy (MDT) of all metastatic sites with or without systemic therapy as an alternative to systemic treatment alone [39–41]. It should also be recognised that many patients enrolled in the completed high-risk localised trials of RT with or without adjuvant therapy would have had PSMA PET–positive disease not evident on conventional scans. It is possible that these "micrometastatic lesions" are managed by systemic therapy along with prostate radiation leading to the survival benefit of adding hormonal therapy to radiation over hormonal therapy or radiation alone [42–44].

**Q12.** For patients with clinically localised prostate cancer without metastases evident on conventional imaging but with positive para-aortic lymph nodes measuring <1 cm on PSMA PET imaging, 25% of panellists voted for treating them as M0, 48% voted for treating them as M0 and add MDT, and 27% voted for treating them as M1. (No consensus for any given answer option.)

**Q13.** For patients with clinically localised prostate cancer who are M0 on conventional imaging but who have one to three PSMA-positive bone lesions, 50% of panellists voted for treating them as M0 and add MDT, 37% voted for treating them as M1, and 13% voted for treating them as M0. (No consensus for any given answer option.)

Previously, STAMPEDE trial investigators reported on the efficacy of prostate RT in addition to androgen deprivation therapy (ADT) in patients with mHSPC with low-burden disease according to conventional imaging [45,46]. Radiation was administered only to the prostate, and participants received a lower biologically effective RT dose than what is commonly used in localised disease (55 Gy in 20 fractions or 36 Gy in six fractions vs 78–80 Gy in 39–40 fractions or 60 Gy in 20 fractions). Other studies also have evaluated [47,48] or are evaluating [49] the efficacy of prostate RT in patients with metastatic prostate cancer.

**Q14.** Regarding the recommended radiation schedule for the primary tumour in patients with high-risk prostate cancer and one to three PSMA-positive bone lesions without a correlate on conventional imaging, 62% of panellists voted for 78–80 Gy in 39–40 fractions (or equivalent hypofrac-

tionated schedules) and 38% voted for 55 Gy in 20 fractions or 36 Gy in six fractions (STAMPEDE). (No consensus for any given answer option.)

For patients with localised high-risk prostate cancer, international guidelines recommend treatment with RT to the prostate in combination with long-term (2–3 yr) ADT with RP in combination with extended pelvic lymph node dissection (PLND) as another treatment option for selected patients as part of multimodal therapy [5,6].

Recent results from the STAMPEDE trial platform combined data from two arms: clinically node-positive patients (cN1 M0) and high-risk node-negative patients (defined as having two or more of the following characteristics: clinical stage ≥cT3, Gleason score [GS] ≥8, and PSA ≥40 ng/ml) [50]. Of note, this high-risk definition is different from the classical "high-risk". Combined therapy with ADT plus androgen receptor pathway inhibitors (ARPIs) produced a clear survival benefit, introducing a new standard of care. Conventional imaging was used for staging. RT to the prostate was required for patients with node-negative disease and encouraged for those with node-positive disease, and was administered in 99% of cN0 and 71% of cN1 patients. In all, 1974 patients were randomised to receive 3 yr of ADT alone (control arm) or 3 yr of ADT plus 2 yr of abiraterone with or without enzalutamide (experimental arms). The experimental arms showed improved metastasis-free survival (MFS) and overall survival (OS) compared with the control arm (hazard ratio [HR] for MFS 0.54, 95% CI 0.43–0.68; HR for OS 0.6, 95% CI 0.48–0.73) [50]. However, compared with adding abiraterone alone to ADT, triple therapy with enzalutamide added to abiraterone and ADT conferred no additional clinical benefit and was associated with greater toxicity [50]. In light of these results, the most recent EAU guidelines recommend offering 2 yr of abiraterone plus ADT when providing definitive RT to the prostate for patients with M0 high-risk disease, including those with cN1 disease [6].

Some guidelines recommend considering the addition of docetaxel to RT and long-term ADT for patients with high-risk prostate cancer, although docetaxel has no proven OS benefit in this setting [5,51]. In the randomised GETUG-12 trial, in which patients with high-risk prostate cancer received either four cycles of docetaxel-estramustine and 3 yr of ADT, or 3 yr of ADT alone, recurrence-free survival (RFS) was superior in the intervention arm (HR 0.71, 95% CI 0.54–0.94; $p = 0.017$) [52]. In the randomised RTOG 0521 trial, the addition of six cycles of docetaxel to prostate RT and 2 yr of ADT improved OS from 89% to 93% at 4 yr, with improved disease-free survival and reduction in the rate of distant metastasis, when compared with prostate RT plus ADT alone [53]. In two prospective randomised Scandinavian Prostate Cancer Group (SPCG) trials, six cycles of docetaxel did not improve biochemical disease-free survival after either prostatectomy (SPCG-12) [54] or radical RT (SPCG-13) [55]. In the SPCG-13 trial, there was a trend towards a treatment benefit from docetaxel in the high-risk (Gleason 9–10) subgroup (HR 0.67, 95% CI 0.34–1.30; $p = 0.2$); follow-up for MFS and OS is on-going [55]. In arm C of the STAMPEDE platform, RFS among patients with high-risk localised or cN1 M0 disease was improved by adding docetaxel to long-term ADT (HR 0.60, 95% CI 0.45–0.80; $p < 0.001$) [56]. A meta-analysis also identified an RFS improvement with docetaxel in patients with high-risk localised prostate cancer (HR 0.70, 95% CI 0.61–0.81; $p < 0.0001$), but OS data were immature at publication [57].

**Q15.** When asked *what systemic therapy they would add to local RT* for patients who are *N0 M0* on next-generation imaging and have *high-risk localised* GS 8–10 [50], 78% of panellists voted for 2–3 yr of ADT plus 2 yr of abiraterone, 22% voted for 2–3 yr of ADT alone, and 1% voted for 2–3 yr of ADT plus six cycles of docetaxel. There were two abstentions. (Consensus to add ADT plus abiraterone.)

**Q16.** When asked *what systemic therapy they would add to local RT* for patients who are *N0 M0* on next-generation imaging and have *very high-risk localised* prostate cancer based on the NCCN definition (one or more of the following: cT3b-cT4, primary Gleason pattern 5, two or three high-risk features, and more than four cores of International Society of Urological Pathology [ISUP] grade group 4 or 5) [5], 78% of panellists voted for 2–3 yr of ADT plus 2 yr of abiraterone, 17% voted for 2–3 yr of ADT alone, and 5% voted for 2–3 yr of ADT plus six cycles of docetaxel. There were three abstentions. (Consensus to add ADT plus abiraterone.)

**Q17.** Among those panellists who recommended adding ADT plus abiraterone, 66% voted that if a patient has contraindication(s) against abiraterone plus prednisone/prednisolone, it is appropriate to replace abiraterone with a novel androgen receptor (AR) antagonist (apalutamide, darolutamide, or enzalutamide), while 34% voted that this is inappropriate. There were 14 abstentions. (No consensus for any given answer option.)

There are various types and schedules of RT to the prostate [58–60]. Hypofractionation offers the advantage of being more convenient for patients at a lower cost. A systematic review of studies of moderate hypofractionation (2.5–3.4 Gy/fraction) concluded that there was sufficient follow-up to support its safety [61]. A recent Cochrane review concluded that survival would be similar irrespective of whether external beam radiotherapy (EBRT) consisted of a moderately hypofractionated regimen or conventional fractionation (HR 1.00, 95% CI 0.72–1.39) [62].

In the ASCENDE-RT trial, which enrolled patients with intermediate- and high-risk prostate cancer, pelvic irradiation (total dose 46 Gy) followed by a low-dose-rate (LDR) brachytherapy boost (total prescribed RT dose 115 Gy) improved 5- and 7-yr PSA progression-free survival (PFS) compared with dose-escalated EBRT (total dose 78 Gy; 89% and 86% vs 84% and 75%, respectively) [63]. This improvement was achieved at the cost of an increase in late grade 3 or worse genitourinary toxicity (18% among patients who received the brachytherapy boost vs 8% in the comparator arm) [63].

High-dose-rate (HDR) brachytherapy delivers radiation directly to the prostate by temporarily introducing a radioactive source. HDR brachytherapy is often administered as a boost in combination with EBRT of at least 45 Gy [64]. Evidence suggests that outcomes with EBRT plus HDR brachytherapy are superior to EBRT alone [65–67].

Ultrahypofractionation regimens (>6 Gy per fraction, usually delivered in four to seven fractions), which usually

are delivered using stereotactic body radiation therapy (SBRT) techniques, are another emerging treatment option for patients with localised prostate cancer [68]. In a systematic review and meta-analysis, 5- and 7-yr rates of biochemical RFS (bRFS) after SBRT were 95.3% and 93.7%, respectively, and estimated rates of late grade 3 or worse genitourinary and gastrointestinal toxicities were 2% and 1.1%, respectively [69]. Two randomised studies were not included in the meta-analysis [70,71]. Although many experts recommend ultrahypofractionation with SBRT for patients with low- and intermediate-risk localised prostate cancer, its role in treating high-risk or very-high-risk prostate cancer is more controversial—while attractive, evidence for efficacy is scant.

**Q18.** When asked which RT regimen they recommend when treating the primary tumour in patients with *high/very-high-risk localised* prostate cancer, 23% of panellists voted for EBRT alone, 35% voted for a moderately hypofractionated regimen of EBRT, 38% voted for EBRT plus a brachytherapy boost, and 4% voted for SBRT. There were 36 abstentions. (No consensus for any given answer option.)

Only low-level evidence supports the use of whole pelvic RT in intermediate- and high-risk localised cN0 prostate cancer; no randomised trial has shown that prophylactic irradiation of the pelvic lymph nodes improves OS in this setting. In the GETUG 01 trial ($n$ = 446), irradiating both the pelvic nodes and the prostate, compared with prostate-only RT, did not significantly improve event-free survival or OS among high-risk patients [72]. In the randomised NRG/RTOG 9413 trial, ADT plus whole pelvic RT significantly improved PFS when compared with ADT plus prostate-only RT among patients with intermediate- and high-risk prostate cancer, but was also associated with more grade 3 or worse late gastrointestinal adverse events (7% vs 2%) [73]. Moreover, neither trial linked elective pelvic RT with an unequivocal, statistically significant benefit in OS or MFS [72,73]. In another recent randomised study, whole pelvic RT significantly improved 5-yr distant MFS (95.9% vs 89.2%, HR 0.35; $p$ = 0.01) and 5-yr disease-free survival (89.5% vs 77.2%; $p$ = 0.02) compared with prostate RT alone, but also resulted in greater toxicity—rates of grade 2 or worse late genitourinary adverse events were 17.7% versus 7.5% ($p$ = 0.02) [74].

**Q19.** For patients with *high/very high-risk localised* prostate cancer (cN0 on *conventional imaging*) who are undergoing RT of the prostate, 83% of panellists voted for irradiating the pelvic nodes and 17% voted against it. There were 21 abstentions. (Consensus for irradiation of pelvic nodes.)

**Q20.** For patients with *high/very high-risk localised* prostate cancer (cN0 on PSMA PET) who are undergoing RT of the prostate, 73% of panellists voted for and 27% voted against irradiation of the pelvic nodes. There were 16 abstentions. (No consensus for any given answer option.)

Approximately 5–10% of patients with prostate cancer have synchronous pelvic nodal metastases on conventional imaging, without evidence of distant metastases (stage cN1 M0) [6]. In a randomised study, staging with PSMA-PET/CT detected pelvic nodal metastases with 32% greater accuracy than conventional imaging among patients with high-risk prostate cancer [9]. One option for treating patients staged as cN1 M0 is to combine locoregional RT with 2–3 yr of ADT; RP with PLND can also be considered for selected individuals as part of multimodal therapy [5,6]. Patients with cN1 M0 prostate cancer were included in the previously mentioned comparisons in the STAMPEDE trial, in which adding 2 yr of abiraterone/prednisone to ADT plus RT was associated with a statistically significant improvement in OS [50].

**Q21.** For patients with newly diagnosed prostate cancer who are *cN1 (pelvic lymph nodes) on conventional imaging*, 73% of panellists voted to recommend treatment with RT plus ADT plus 2 yr of abiraterone, 20% voted for surgery as the first step of multimodal therapy, and 7% voted for RT plus ADT. There were four abstentions. (No consensus for any given answer option, but combined 80% voted for RT plus some form of hormonal treatment.)

**Q22.** For patients with prostate cancer who are cN0 on conventional imaging but have *positive pelvic lymph nodes without distant lesions (M0) on PSMA PET*, 58% of panellists voted for treatment with RT plus ADT plus 2 yr of abiraterone, 24% voted for surgery as the first step of multimodal therapy, and 18% voted for RT plus ADT. There were ten abstentions. (No consensus for any given answer option, but combined 76% voted for RT plus some form of hormonal treatment.)

The goal of adjuvant RT (aRT) is to decrease the risk of relapse in patients undergoing RP. In a retrospective study of 1338 patients with confirmed regional lymph node metastases (pN1) after RP, aRT plus ADT was associated with a statistically significant improvement in OS compared with observation or ADT alone [75]. For patients with pN1 prostate cancer who have undetectable PSA after RP with extended PLND, a number of factors can help inform the decision to offer aRT, including pathological tumour status (pT), pathological margin involvement, ISUP grade group, and the number of involved lymph nodes [6]. For pN1 patients, cancer mortality seems to rise drastically when three or more lymph nodes are positive (pathological) [75–78], and it is in such a high-risk setting that aRT might confer the most benefit. In an observational study of the National Cancer Database, among >8000 patients who were pN1 after RP, aRT in addition to ADT was associated with a statistically significant improvement in OS, which was particularly pronounced among patients with adverse pathological features ($\geq$pT3b disease, GS $\geq$9, more than three positive lymph nodes, or positive surgical margins) [79]. In another observational study of 5498 patients with pN1 prostate cancer, aRT plus ADT was associated with an OS benefit only among patients with either (1) one to two positive nodes, pathological GS 7–10, and pT3b/4 disease or positive surgical margins, or (2) three to four positive nodes, regardless of local tumour characteristics [80].

**Q23.** For patients with *one or two pathologically involved pelvic lymph nodes* following radical surgery with extended PLND (pN1 and *no high-risk features*: ISUP grade group 4–5 or pT3 or positive margins) *who have no evidence of metastases on preoperative staging* and undetectable postoperative PSA, provided that continence has been regained, 81% of panellists voted for monitoring alone and salvage therapy only in case of a PSA rise, 15% voted for aRT plus systemic

hormonal treatment, 3% voted for systemic hormonal treatment alone, and 1% voted for aRT. There were three abstentions. (Consensus for monitoring alone with salvage therapy in case of a PSA rise.)

**Q24.** For patients with *one or two pathologically involved pelvic lymph nodes* following radical surgery with extended PLND (pN1 and *two or more out of three high-risk features*: ISUP grade group 4–5 or pT3 or positive margins) *who have no evidence of metastases on preoperative staging* and undetectable postoperative PSA, provided that continence has been regained, 48% of panellists voted for monitoring alone and salvage therapy only in case of a PSA rise, 42% voted for aRT plus systemic hormonal treatment, 5% voted for aRT alone, and 5% voted for systemic hormonal treatment alone. There were three abstentions. (No consensus for any given answer option.)

**Q25.** For patients with *three or more pathologically involved pelvic lymph nodes* following radical surgery with extended PLND (pN1 and *no high-risk features*: ISUP grade group 4–5 or pT3 or positive margins) *who have no evidence of metastases on preoperative staging* and undetectable postoperative PSA, provided that continence has been regained, 46% of panellists voted for treatment with aRT plus systemic hormonal treatment, 45% voted for monitoring alone and salvage therapy only in case of a PSA rise, 7% voted for systemic hormonal treatment alone, and 2% voted for aRT alone. There were five abstentions. (No consensus for any given answer option.)

**Q26.** For patients with *three or more pathologically involved pelvic lymph nodes* following radical surgery with extended PLND (pN1 and *two or more out of three high-risk features*: ISUP grade group 4–5 or pT3 or positive margins) *who have no evidence of metastases on preoperative staging* and undetectable postoperative PSA, provided that continence has been regained, 50% of panellists voted for treatment with aRT plus systemic hormonal treatment, 38% voted for monitoring alone and salvage therapy only in case of a PSA rise, 8% voted for systemic hormonal treatment alone, and 4% voted for aRT alone. There were four abstentions. (No consensus for any given answer option.)

Several studies have evaluated the management of patients with prostate cancer who do not have pathological lymph node involvement (pN0). In four prospective randomised clinical trials, aRT after RP delayed BCR among patients who were pN0 and high risk (≥pT3 with positive surgical margins and GS ≥8) [81–84]. A Cochrane review concluded that for patients who are pN0, adjuvant ADT after RP with extended PLND is associated with a possible PFS benefit but no OS benefit [85].

Three completed prospective randomised trials, RADICALS, RAVES, and GETUG-AFU 17, have compared aRT with early salvage radiotherapy (sRT) with or without ADT [86–88]. None of these studies found a statistically significant effect on BCR, but the results merit cautious interpretation because <20% of enrolled patients had high-risk features; indeed, even the prospectively planned ARTISTIC meta-analysis of these trials might have been underpowered [6,89].

**Q27.** For patients at *high risk of relapse following RP* (R0) and extended PLND who have *undetectable postoperative PSA* and with both *Gleason 8–10 and pT3b/T4 but pN0*, provided that continence has been regained, 84% of panellists voted for initial monitoring and early sRT with or without systemic hormonal treatment in case of PSA rise, and 16% voted for immediate aRT with or without systemic hormonal treatment. There were six abstentions. (Consensus for monitoring and early salvage therapy in case of PSA rise.)

**Q28.** For patients at *high risk of relapse following RP* and extended PLND who have *undetectable postoperative PSA* and are *R1 and both Gleason 8–10 and pT3b/T4, but who are pN0*, provided that continence has been regained, 63% of panellists voted for initial monitoring and early sRT with or without systemic hormonal treatment in case of PSA rise, and 37% voted for immediate aRT with or without systemic hormonal treatment. There were six abstentions. (No consensus for any given answer option.)

**Q29.** For patients at *high risk of relapse following RP* plus extended PLND who have *adverse pathological factors* (R0 or R1, Gleason 8–10, and pT3b/T4; pN0) and *undetectable postoperative PSA*, 67% of panellists voted for and 33% voted against adding systemic hormonal treatment when performing aRT. There were 19 abstentions. (No consensus for any given answer option.)

Molecular classifiers, including Oncotype DX Prostate Cancer Assay, Prolaris, and Decipher, seem to be promising for identifying additional biomarkers that might help guide treatment decisions [90–93]. Prospective randomised clinical trials are required to validate their utility, but according to current NCCN guidelines, their use can be considered in selected patients in combination with all other established clinic-pathological markers [6].

**Q30.** Outside of a clinical trial, for patients with *low-risk* localised prostate cancer, 67% of panellists voted against the use of a molecular classifier (eg, Decipher, Prolaris, or Oncotype DX prostate), 30% voted for it in selected cases where results would influence treatment decision, and 3% voted for it in the majority of patients. There were 17 abstentions. (No consensus for any given answer option.)

**Q31.** Outside of a clinical trial, for patients with *favourable intermediate-risk* (NCCN) localised prostate cancer, 54% of panellists voted against the use of a molecular classifier (eg, Decipher, Prolaris, or Oncotype DX prostate), 39% voted for it in selected cases where results would influence treatment decision, and 7% voted for it in the majority of patients. There were 18 abstentions. (No consensus for any given answer option.)

**Q32.** Outside of a clinical trial, for patients with *unfavourable intermediate-risk* (NCCN) localised prostate cancer, 59% of panellists voted against the use of molecular classifier (eg, Decipher, Prolaris, or Oncotype DX prostate), 23% voted for it in selected cases where results would influence treatment decision, and 18% voted for it in the majority of patients. There were 19 abstentions. (No consensus for any given answer option.)

**Q33.** Outside of a clinical trial, for patients with *high-risk localised prostate cancer*, 62% of panellists voted against the use of a molecular classifier (eg, Decipher, Prolaris, or Oncotype DX prostate), 26% voted for it in selected cases where the results would influence treatment decision, and 12%

voted for it in the majority of patients. There were 18 abstentions. (No consensus for any given answer option.)

### 2.1. Discussion of part 1: intermediate- and high-risk and locally advanced prostate cancer

Currently, we have no evidence that more accurate staging improves relevant clinical outcomes in advanced prostate cancer. Nonetheless, APCCC 2022 panellists reached consensus to use next-generation imaging, specifically PSMA PET, for staging patients with high-risk localised disease. They also reached consensus not to use PSMA PET for staging patients with favourable intermediate-risk disease. For unfavourable intermediate-risk patients, about half of panellists supported the use of PSMA PET for staging, while the other half did not. In contrast, there was strong consensus regarding not to use whole-body MRI for staging. There was consensus that the TNM classification should be refined to take into account the results of next-generation imaging (Table 1).

Although there was no consensus regarding the preferred radiation schedule for treating high-risk and very-high-risk patients, only 4% of panellists voted for SBRT for these individuals. This result reflects the fact that clinical trials of SBRT primarily enrolled patients with low- and intermediate-risk prostate cancer. Several on-going trials (TROG 1801, ASSERT, and PACE-C) are assessing the role of SBRT in intermediate- and high-risk prostate cancer and should yield informative results within the next several years.

There was consensus to offer elective RT of the pelvic nodes when patients are cN0 by conventional imaging. Most panellists also voted for pelvic nodal RT in patients who are cN0 by PSMA PET. Of note, elective nodal RT in high-risk patients remains a matter of controversy due to a lack of unequivocal evidence of a significant OS benefit. Among the three relevant published phase 3 trials, only one (POP-RT) demonstrated a statistically significant improvement in MFS and none identified a significant OS benefit [72–74]. This could be due to patient selection, staging methods, treatment volumes, or radiation dose and interaction with ADT. Forthcoming results from the RTOG 0924, GETUG-AFU 23, and UK PIVOTAL-boost trials will help better define the role of whole pelvic RT (ie, irradiation of the pelvic lymph nodes, in addition to the prostate) in patients with high-risk prostate cancer.

There was no consensus on how to treat patients who are M0 on conventional imaging but have positive lesions on PSMA PET; about 10% of panellists voted that they would alter management depending on the PSMA PET status of regional lymph nodes. As previously stated, when patients have metastatic disease detected only by next-generation imaging, including PSMA PET, therapeutic decisions should be made with caution, because evidence on ideal management is not available [32]. Although it is possible that the use of PSMA PET for staging may improve clinical outcomes by optimising the use of local and/or adjuvant systemic therapy, this has yet to be proved [94]. Moreover, work is needed to define what level of risk of metastatic disease is sufficient to warrant staging by PSMA PET—that is, what pretest probability of metastases overcomes the risk of false positives and resultant potential for harmful mismanagement or overtreatment.

For patients who are cN1 and are at a high risk or very high risk, there was consensus to add 2 yr of abiraterone/prednisone when administering systemic treatment. This is in keeping with recently published data from the STAMPEDE trial [50].

Some trials have demonstrated the therapeutic equivalence of early sRT and aRT [86–88], but only a minority of the included patients had high-risk disease. About half of panellists supported aRT if three or more lymph nodes were involved and/or if high-risk features were present, suggesting that, in the absence of data from specifically designed trials, aRT will continue to play a role in the treatment of selected patients at a high risk of relapse. Recent retrospective evidence on aRT in patients with pN1 prostate cancer supports its use while highlighting the need to personalise therapy based on the number of positive pelvic nodes and other risk factors [95]. However, patients can also have pN0 disease and be at a high risk of relapse. Interestingly, a majority of panellists voted for early sRT for such patients, even though they were under-represented in the three completed randomised trials comparing early sRT with aRT. In the future, genomic classifiers may be helpful for selecting patients who would likely benefit from aRT. At APCCC 2022, however, the majority of panellists voted against the use of genomic classifiers for patients with localised disease outside the setting of clinical trials, independent of the risk category.

## 3. PSA persistence and BCR

PSA persistence is defined in most studies as detectable PSA $\geq$0.1 ng/ml within 4–8 wk after RP [96,97]. Several studies have linked PSA persistence with more advanced disease (positive surgical margins, pathological stage >T3a, positive nodal status, or pathological ISUP grade >3) and poor prognosis [98–100]. Conventional imaging has low accuracy for detecting the presence of prostate cancer in the setting of low PSA values, while PSMA PET can identify residual cancer even at very low PSA values, especially for PSA >0.2 ng/ml [101,102]. Based on these considerations, international guidelines recommend performing PSMA PET for patients with prostate cancer with postoperative persistent PSA >0.2 ng/ml if the results influence subsequent treatment decisions [6].

For patients with PSA persistence, the benefit of sRT with or without ADT remains unclear—no trials have specifically addressed this question. The presence of risk factors (microscopic disease at the primary tumour site [R1], pT3, and ISUP grade group 4–5) in patients with prostate cancer with PSA persistence may influence clinical outcomes and therefore also treatment choice. One systematic review concluded that for patients with PSA persistence, sRT with or without ADT seemed to be associated with improved survival outcomes [97]. In another small study, addition of 2 yr of ADT to sRT achieved encouraging results in 78 patients who had PSA persistence with pT3 and/or R1 disease after RP [103]. In the GETUG-22 phase 2 trial, which evaluated RT with or without short-term ADT in patients with PSA

**Table 1 – APCCC 2022 questions concerning intermediate- and high-risk and locally advanced prostate cancer that have reached consensus**

| Question | Answers | Voting results, % (*n*) |
|---|---|---|
| 1. Are you in favour of refining the metastatic classification (N and M) in TNM to have a notation for PSMA PET–positive lesions (eg, as suggested by the PROMISE paper)? | 1. Yes | 87 (89), consensus |
| | 2. No | 13 (13) |
| 2. Do you recommend PSMA PET in the majority of patients with clinically localised high-risk localised prostate cancer? | 1. Yes | 77 (79), consensus |
| | 2. No | 23 (23) |
| 4. Do you recommend PSMA PET in the majority of patients with clinically localised favourable intermediate-risk (NCCN definition) localised prostate cancer? | 1. Yes | 8 (8) |
| | 2. No | 92 (95), strong consensus |
| 5. If you recommend PSMA PET for systemic staging of clinically localised prostate cancer, what do you recommend (in addition to the MRI of the prostate)? | 1. PSMA PET only after conventional imaging negative or indeterminate | 22 (19) |
| | 2. Upfront PSMA PET with or without subsequent conventional imaging | 78 (66), consensus |
| 6. In the majority of patients with clinically localised prostate cancer and PSMA positivity, with metastasis-consistent findings in the bone on the CT part of upfront PSMA PET, do you recommend any additional imaging (eg, MRI, bone scintigraphy)? | 1. Yes | 22 (22) |
| | 2. No | 78 (80), consensus |
| 8. Do you recommend whole-body, diffusion-weighted MRI for systemic staging in the majority of patients with clinically localised high-risk prostate cancer? | 1. Yes | 9 (9) |
| | 2. No | 91 (93), strong consensus |
| 9. Do you recommend whole-body, diffusion-weighted MRI for systemic staging in the majority of patients with clinically localised intermediate-risk prostate cancer? | 1. Yes | 5 (5) |
| | 2. No | 95 (97), strong consensus |
| 15. In the majority of patients with high-risk localised (STAMPEDE definition) prostate cancer (≥2 out of 3 criteria: cT3/T4, PSA ≥40, Gleason 8–10) and N0 M0 on next-generation imaging, what is your recommended systemic therapy in combination with local radiation therapy? | 1. ADT alone for 2–3 yr | 21 (22) |
| | 2. ADT for 2–3 yr plus abiraterone for 2 yr | 78 (80), consensus |
| | 3. ADT for 2–3 yr plus docetaxel 6 cycles | 1 (1) |
| 16. In the majority of patients with very-high-risk localised prostate cancer (NCCN definition: at least one of the following: cT3b-cT4, primary Gleason pattern 5, 2 or 3 high-risk features, >4 cores of ISUP grade group 4 or 5) and N0 M0 on next-generation imaging, what is your recommended systemic therapy in combination with radiation therapy to the primary? | 1. ADT alone for 2–3 yr | 17 (17) |
| | 2. ADT for 2–3 yr plus abiraterone for 2 yr | 78 (80), consensus |
| | 3. ADT for 2–3 yr plus docetaxel 6 cycles | 5 (5) |
| 19. In the majority of patients with high/very-high-risk localised prostate cancer (cN0 on conventional imaging) undergoing RT of the prostate, do you recommend irradiation to pelvic nodes? | 1. Yes | 83 (70), consensus |
| | 2. No | 17 (14) |
| 23. For the majority of patients with 1 or 2 pathologically involved pelvic lymph nodes following radical surgery with extended PLND (pN1 and no high-risk features: ISUP grade group 4–5 or pT3 or positive margins) without evidence of metastases on preoperative staging, with undetectable postoperative PSA, what is your recommendation provided the patient has regained continence? | 1. Monitoring alone and salvage therapy in case of PSA rise | 81 (83), consensus |
| | 2. Adjuvant radiation therapy | 1 (1) |
| | 3. Adjuvant radiation therapy plus systemic hormonal treatment | 15 (15) |
| | 4. Systemic hormonal treatment alone | 3 (3) |
| 27. For the majority of patients with a high risk of relapse following radical prostatectomy (R0), extended PLND, and undetectable postoperative PSA, and with both Gleason 8–10 and pT3b/T4 but pN0, which treatment do you recommend provided the patient has regained continence? | 1. Immediate adjuvant RT ± systemic hormonal treatment | 16 (16) |
| | 2. Monitoring and early salvage RT ± systemic hormonal treatment if PSA rises | 84 (83), consensus |

ADT = androgen deprivation therapy; APCCC = Advanced Prostate Cancer Consensus Conference; CT = computed tomography; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PET = positron emission tomography; PLND = pelvic lymph node dissection; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RT = radiation therapy; TNM = tumour, node, metastasis.

persistence after surgery, combination therapy was well tolerated but oncological endpoints were unpublished as of this writing [104,105]. In the phase 2/3 EMPIRE-1 trial, which included 165 patients with PSA persistence and negative conventional imaging after RP, the incorporation of fluciclovine $^{18}$F-PET into postsurgery RT decision-making and planning was associated with a significant improvement in bRFS and PSA persistence-free survival; OS data are pending [106]. The panel discussed questions around PSA persistence and biochemical recurrence (see Table 2 and supplement 2 for details).

**Q34.** For patients with *PSA persistence 4–8 wk after RP* (pN0) who are M0 on preoperative imaging, 91% of panellists voted to recommend PSMA PET and 9% voted not to recommend it. There were six abstentions. (Strong consensus for PSMA PET.)

**Q35.** For patients with *PSA persistence 4–8 wk after RP* (pN0 with *no evidence of risk factors* (R1, pT3, or ISUP grade

group 4–5) who were M0 on preoperative imaging and have negative postoperative PSMA PET, provided that continence has been regained, 54% of panellists voted for treatment with sRT plus systemic hormonal treatment, 18% voted for sRT alone, and 28% voted for PSA surveillance without immediate active treatment. There were six abstentions. (No consensus for any given answer option.)

**Q36.** For patients with *PSA persistence 4–8 wk after RP* (pN0 and *two or more risk factors*: R1, pT3, and ISUP grade group 4–5) who were M0 on preoperative imaging and have negative postoperative PSMA PET, provided that continence has been regained, 77% of panellists voted for treatment with sRT plus systemic hormonal treatment, 12% voted for PSA surveillance without immediate active treatment, 10% voted for sRT alone, and 1% voted for systemic hormonal treatment alone. There were six abstentions. (Consensus for sRT plus systemic hormonal treatment.)

Historically, BCR after RP was defined as a rising PSA level with an absolute value of ≥0.2 ng/ml, which was confirmed by a second measurement [107]. However, this definition has been changed recently; both NCCN and EAU guidelines have eliminated the 0.2 ng/ml threshold and defined BCR as two or more increases in a PSA level that was previously undetectable [5,6]. For patients with BCR, the guidelines recommend PSMA PET if the results influence subsequent treatment decisions (of note, the EAU recommends that PSA be ≥0.2 ng/ml before a PSMA PET scan is performed) [5,6]. It should be recognised that for PSA levels in this range, PSMA PET would have a low but not zero probability of detecting recurrence [106].

Based on the EAU classification, patients with prostate cancer with BCR after RP can be categorised as having a low risk (PSA doubling time [PSA-DT] >1 yr and pathological ISUP grade <4 for RP) or a high-risk (PSA-DT ≤1 yr or pathological ISUP grade 4–5 for RP) [6,108]. This classification system was further validated by an analysis of data from 1125 patients with post-RP BCR [109]. Among patients who have a low risk according to the EAU classification, monitoring PSA values may remain an option.

**Q37.** When asked at what confirmed rising PSA level, the panel recommended a PSMA PET after RP in patients with PSA-DT >1 yr and a pathological ISUP grade group of <4 (*EAU low-risk category*) [80], 69% of panellists voted for >0.2–0.5 ng/ml, 21% voted for >0.5 ng/ml, 4% voted for <0.2 ng/ml, and 6% voted that they do not recommend imaging in this setting. There were three abstentions. (No consensus for any given answer option.)

**Q38.** For patients with rising PSA after RP and PSA-DT >1 yr, a pathological ISUP grade group of <4 (EAU low-risk category), and negative PSMA PET, 47% of patients voted for treatment with sRT with or without systemic therapy; 28% voted for active monitoring, with treatment only if a positive lesion is seen on follow-up PSMA PET; and 25% voted for sRT with or without systemic therapy only in the context of additional adverse pathological factors (eg, R1, T3/T4, or molecular classifier). There were two abstentions. (No consensus for any given answer option.)

**Q39.** For patients with rising PSA after RP and PSA-DT >1 yr and a pathological ISUP grade group of <4 (EAU low-risk category), and when PSMA PET imaging is not available, 28% of panellists voted for treatment with sRT plus systemic therapy, 27% voted for sRT alone, 25% voted for sRT with or without systemic therapy only in the context of additional adverse pathological factors (eg, R1, T3/T4, or molecular classifier), and 20% voted for active monitoring, with treatment only if a positive lesion is seen on follow-up imaging. There were two abstentions. (No consensus for any given answer option; a combined total of 80% voted for sRT.)

In addition to PSA-DT and ISUP grade, time from RP until BCR and local disease characteristics (surgical margin, pT status, and pN status) are important prognostic factors that can affect treatment choice and timing in patients with BCR after RP [110,111]. According to EAU guidelines, patients with two consecutive increases in PSA after RP who need salvage therapy should be offered early sRT; a negative PSMA-PET scan should not delay sRT, and sRT should be started as soon as possible without waiting until PSA reaches a specific threshold [6].

**Q40.** For patients with *rising PSA after RP* with risk factors for local relapse (defined as ≥pT3b and/or R1) and PSA-DT <1 yr or a pathological ISUP grade group of 4–5 (*EAU high-risk category*), 60% of panellists voted to treat as early as possible (ie, before PSA <0.2 ng/ml) with sRT with or without systemic therapy, and 40% voted to wait until PSA is ≥0.2 ng/ml and perform imaging. There were four abstentions. (No consensus for any given answer option.)

**Q41.** For patients with *rising PSA after RP* without risk factors for local relapse (defined as ≥pT3b and/or R1) and PSA-DT <1 yr or a pathological ISUP grade group of 4–5 (*EAU high-risk category*), 53% of panellists voted for waiting until PSA is ≥0.2 ng/ml and performing PSMA PET, 45% voted for performing sRT with or without systemic therapy as early as possible (ie, before PSA reaches 0.2 ng/ml), and 2% voted for treatment with systemic therapy alone. There were five abstentions. (No consensus for any given answer option.)

In case of a PSA level of <0.2 ng/ml, the probability that PSMA-PET is positive is approximately 33%, while this percentage rises to 45% when PSA is 0.2–0.5 ng/ml [101]. Recently, the CONDOR study demonstrated higher rates of positivity with $^{18}$F-DCFPyL-PET imaging (36.2% when PSA <0.5 ng/ml and 96.7% when PSA ≥5 ng/ml) [14]. Importantly, guidelines suggest performing PSMA-PET in patients with BCR when PSA is >0.2 ng/ml but not waiting for a positive result if salvage treatment is being considered [6].

**Q42.** When asked at what PSA level the panel recommend PSMA PET imaging for patients with *rising PSA after RP* and PSA-DT <1 yr or a pathological ISUP grade group of 4–5 (*EAU high-risk category*), 80% of panellists voted for >0.2–0.5 ng/ml, 11% voted for <0.2 ng/ml, and 9% voted for >0.5 ng/ml. There were seven abstentions. (Consensus for PSMA PET when PSA >0.2–0.5 ng/ml.)

Salvage RT has been found to improve disease control in patients with BCR after RP [112,113]. The question of additional systemic therapy was addressed by three large randomised trials. In RTOG 9601, OS was marginally superior when patients received 2 yr of bicalutamide (150 mg daily) plus sRT as compared with sRT alone [114]. In GETUG-AFU 16, sRT plus 6 mo of ADT improved biochemical PFS but not OS [115]. More recently, in the randomised multicentre

three-group SPPORT trial, short-term (4–6 mo) ADT in addition to sRT of the pelvic lymph nodes and the prostate bed led to a significant improvement in freedom from BCR compared with prostate bed–only RT with or without short-term ADT [116]. At the time of APCCC 2022, the results of the RADICALS-HD trial and the DADSPORT meta-analysis, which were recently presented at European Society for Medical Oncology (ESMO) in 2022, were not available [117].

**Q43.** For patients with *rising PSA after RP* and PSA-DT <1 yr, or a pathological ISUP grade group of 4–5 (*EAU high-risk category*) and negative PSMA PET, 71% of panellists voted for treatment with sRT with or without systemic therapy; 19% voted for sRT with or without systemic therapy only in the context of additional adverse pathological factors (eg, R1, T3/T4, or molecular classifier); 7% voted for active monitoring, with treatment only if a positive lesion is seen on follow-up PSMA PET; and 3% voted for systemic therapy alone (including intermittent therapy). There were five abstentions. (No consensus for any given answer option; a combined total of 90% voted for sRT, at least in the context of adverse factors.)

**Q44.** For patients with *rapidly rising PSA (eg, PSA-DT <3 mo) after RP* who have an ISUP grade group of 4–5 and/or pT3/4 disease, if PSMA PET imaging is either negative or unavailable, 75% of panellists voted for treatment with sRT plus systemic therapy; 11% voted for systemic therapy alone; 8% voted for active monitoring, with treatment only if a positive lesion is seen on follow-up imaging; and 6% voted for sRT alone. There were five abstentions. (Consensus for sRT plus systemic therapy.)

**Q45.** For patients with *rising PSA after RP* and PSA-DT <1 yr or a pathological ISUP grade group of 4–5 (EAU high-risk category), if PSMA PET imaging is not available, 70% of panellists voted for treatment with RT plus systemic therapy, 17% voted for sRT with or without systemic therapy only in the context of additional adverse pathological factors (eg, R1, T3/T4, or molecular classifier), 7% voted for sRT alone, 4% voted for systemic therapy alone (including intermittent therapy), and 2% voted for active monitoring, with treatment only if a positive lesion is seen on follow-up imaging. There were five abstentions. (No consensus for any given answer option; a combined total of 94% voted for sRT at least in the context of adverse factors.)

Intermittent treatment may be an option for patients with BCR after RP who receive systemic therapy alone. In a phase 3 study of a heterogeneous patient population with locally advanced and relapsed prostate cancer, intermittent ADT appeared to be as effective as continuous ADT but did not improve quality of life [118]. In a study of patients with rising PSA after primary or sRT, intermittent ADT provided potential benefits in physical function, fatigue, urinary problems, hot flashes, libido, and erectile function [119].

**Q46.** When recommending systemic therapy alone for patients with *rising PSA after RP* and negative imaging whose PSA-DT is <1 yr or pathological ISUP grade group is 4–5 (*EAU high-risk category*), 56% of panellists voted for intermittent ADT, 26% voted for continuous ADT, 17% voted for ADT plus an ARPI, and 1% voted for ADT plus docetaxel. There were 32 abstentions. (No consensus for any given answer option.)

In a secondary analysis of data from the RTOG 9601 trial, pre-sRT PSA value appeared to predict the efficacy of adding hormone treatment to sRT [120]. In subgroup analyses, hormone therapy improved outcomes among patients with pre-sRT PSA $\geq$0.7 ng/ml; in contrast, hormone therapy did not improve OS, but appeared to reduce second PSA relapses among patients with pre-sRT PSA <0.7 ng/ml who received early sRT [120]. Of note, patients in this trial received bicalutamide at a daily dose of 150 mg, which has limited global regulatory approval.

**Q47.** For the majority of patients with an RP for intermediate- or high-risk localised prostate cancer and an *early rise in PSA and PSA <0.7 ng/ml*, the panel voted on their preferred treatment in conjunction with sRT to the prostate bed: 61% of panellists voted for 6 mo of systemic hormonal therapy, 16% voted for 2 yr of systemic hormonal therapy, 14% voted for the use of a molecular test (eg, Decipher) to guide this decision, and 9% voted not to add systemic treatment (RT alone). There were nine abstentions. (No consensus for any given answer option; a combined total of 77% voted for sRT in combination with systemic hormonal therapy.)

**Q48.** For the majority of patients with an RP for intermediate- or high-risk localised prostate cancer and an *early rise in PSA and PSA $\geq$0.7 ng/ml*, the panel voted on their preferred treatment option in conjunction with early sRT to the prostate bed: 63% of panellists voted for 6 mo of systemic hormonal therapy, 28% voted for 2 yr of systemic hormonal therapy, 7% voted for the use of a molecular test (eg, Decipher) to guide this decision, and 2% voted not to add systemic treatment. There were seven abstentions. (No consensus for any given answer option; a combined total of 91% voted for sRT in combination with systemic hormonal therapy.)

For patients who complete local treatment and then have pelvic lymph node recurrence(s) captured only on next-generation imaging, MDT may be proposed with the aim of delaying systemic treatment; this approach was demonstrated in a prospective study that used choline PET [39]. Several retrospective studies also evaluated MDT (salvage lymph node resection, elective nodal irradiation, or SBRT) in nodal oligorecurrent prostate cancer detected by PET after RP [121,122]. However, these results need confirmation in larger prospective trials before any recommendations can be made. The STAMPEDE trial enrolled patients with pelvic lymph node recurrence after radical treatment, although these comprised a small percentage of the study population (3%) [50]. For such patients, RT in combination with 2 yr of ADT and abiraterone may be considered. In addition, irradiation of both the prostate bed and the pelvic lymph nodes may improve outcomes in selected patients. In the recent randomised multicentre SPPORT trial of 1792 patients with prostate cancer and BCR after RP, patients who received RT to the prostate bed and the pelvic lymph nodes in addition to short-term ADT experienced a clinically significant improvement in freedom from progression compared with patients who received only prostate bed RT with or without ADT [116].

**Q49.** For patients with *rising PSA after RP (with or without sRT of the prostate bed*) and *one to three positive lymph nodes*

*in the pelvis alone on PSMA PET*, 85% of panellists voted for locoregional treatment plus systemic therapy, 10% voted for locoregional treatment alone, and 5% voted for systemic therapy alone. There were six abstentions. (Consensus for locoregional treatment plus systemic therapy.)

**Q50.** Among the panellists who voted for locoregional treatment in Q49, 92% voted for RT and 8% voted for surgery. There were 13 abstentions. (Strong consensus for RT among the panellists who voted for locoregional treatment.)

In a meta-analysis, after adjusting for clinic-pathological variables, the Decipher genomic classifier remained a statistically significant predictor of metastasis in patients with prostate cancer after RP (HR 1.30, 95% CI 1.14–1.47; $p < 0.001$), suggesting that it could independently improve prognostication [123]. Other analyses using the Decipher genomic classifier have published similar results [90,124]. A systematic review confirmed these results [125]. However, further studies, ideally of a prospective nature, are needed to establish how to best incorporate Decipher into clinical decision-making.

**Q51.** Outside of a clinical trial, for patients with initially undetectable but subsequently rising PSA after RP, 82% of panellists voted against using a molecular classifier (eg, Decipher) and 18% voted to do so. There were ten abstentions. (Consensus not to use a molecular classifier.)

**Q52.** Outside of a clinical trial, for patients with PSA persistence (who never achieved undetectable postoperative PSA) after RP, 80% of panellists voted against using a molecular classifier (eg, Decipher) and 20% voted to do so. There were 11 abstentions. (Consensus not to use a molecular classifier.)

Several randomised clinical trials have demonstrated the efficacy of combining hormone therapy with sRT in patients with BCR after RP [114,115]. In a phase 3 trial of 743 such individuals, 6 mo of ADT plus sRT significantly improved 12-yr PFS compared with sRT alone (64% vs 49%, HR 0.54, 95% CI 0.43–0.68; $p < 0.0001$) but conferred no OS benefit even after >10 yr of follow-up [115]. In the RTOG 9601 trial, in which control therapy was sRT alone, addition of 24 mo of bicalutamide (150 mg/d) to sRT was associated with a significant improvement in 12-yr OS (76.3% vs 71.3%, HR 0.77, 95% CI 0.59–0.99; $p = 0.04$) and lower prostate cancer mortality (5.8% vs 13.4%; $p < 0.001$) [114]. In the recently published RTOG 0534 trial, 5-yr freedom from progression was significantly improved by adding short term (4–6 mo) ADT to prostate bed RT rather than administering prostate bed RT alone [116]. At the time of APCCC 2022, the results of the RADICALS-HD trial and the DADSPORT meta-analysis, which were recently presented at ESMO 2022, were not available [117].

**Q53.** For patients with *rising PSA after RP* who have negative PSMA PET, 43% of panellists voted to recommend systemic treatment in combination with sRT, 23% voted for this combination only for PSA >0.5 ng/ml and/or there are other adverse factors (eg, high GS, rapid PSA-DT, or a high Decipher score), 20% voted for this combination only if there are other adverse factors (eg, high GS, rapid PSA-DT, or a high Decipher score), 7% voted for the combination only if preradiation PSA is >0.5 ng/ml, and 7% voted against the combination. There were seven abstentions. (No consensus for any given answer option; a combined total of 93% voted for systemic therapy at least in selected patients.)

**Q54.** When recommending systemic therapy for patients with rising PSA after RP who have negative PSMA PET, 85% of panellists voted for ADT with a luteinising hormone-releasing hormone (LHRH) agonist or antagonist, 10% voted for ADT plus an ARPI, and 5% voted for bicalutamide monotherapy. There were 11 abstentions. (Consensus for ADT with an LHRH agonist or antagonist among the panellists who voted for systemic therapy.)

**Q55.** When combining *systemic hormonal treatment plus sRT* in patients with rising PSA after RP and a negative PSMA PET scan, 80% of panellists recommended a short-term (eg, 6-mo) AR blockade and 20% recommended a long-term (eg, 18–24 mo) AR blockade. There were ten abstentions. (Consensus for short-term AR blockade among the panellists who voted for systemic therapy.)

In patients who have received definitive RT with or without ADT, BCR is defined according to the Phoenix definition as any PSA increase >2 ng/ml above nadir, where nadir is the lowest PSA achieved after curative treatment [126]. In a prospective multicentre study in which 27% of patients experienced BCR after definitive RT, PSMA-PET showed a high positive predictive value for localising recurrent prostate cancer [12]. Patients with BCR after definitive RT can be classified to have a low risk (interval to biochemical failure >18 mo and GS <8 for RT) or high risk (interval to biochemical failure $\leq$18 mo and GS $\geq$8 for RT) based on the EAU classification [6,108].

**Q56.** For asymptomatic patients with rising PSA after radical (definitive) RT of the prostate whose interval to biochemical failure is >18 mo and biopsy ISUP grade group is <4 (*EAU low-risk category*), 73% of panellists voted for imaging when confirmed PSA level is $\geq$2 ng/ml above nadir and 27% voted for imaging before PSA reaches 2 ng/ml above nadir. There were five abstentions. (No consensus for any given answer option.)

**Q57.** As a first step for imaging in patients with rising PSA after radical RT of the prostate whose interval to biochemical failure is >18 mo and biopsy ISUP grade group is <4 (EAU low-risk category), assuming that all imaging modalities are available, 78% of panellists voted for PSMA PET, 11% voted for MRI of the pelvis alone, 9% voted for CT and/or bone scintigraphy, 1% voted for whole-body MRI alone/choline/fluciclovine PET/CT, and 1% voted that they do not recommend imaging in this setting. There were two abstentions. (Consensus for PSMA PET.)

For patients with BCR after radical RT, therapeutic options include ADT or local salvage procedures; for patients with EAU low-risk BCR features, active follow-up monitoring of PSA values may be a viable option [5,6]. A systematic review and meta-analysis of data from patients with locally recurrent prostate cancer after radical RT found no significant differences in RFS when comparing salvage RP, salvage high-intensity focused ultrasound (HIFU), salvage cryotherapy, SBRT, salvage LDR brachytherapy, and salvage HDR brachytherapy [127].

**Q58.** For *fit* patients with a *confirmed local recurrence in the prostate after radical local RT* with an interval to biochemical failure of >18 mo and biopsy ISUP grade group

<4 (*EAU low risk*) who are suitable for a second definitive treatment and without detectable metastases, 38% of panellists voted for performing salvage prostatectomy, 19% voted for HIFU and/or cryotherapy and/or irreversible electroporation (IRE), 15% voted for brachytherapy, 14% voted for EBRT reirradiation with or without brachytherapy, and 14% voted that they do not recommend a second definitive local treatment option in this setting. There were 12 abstentions. (No consensus for any given answer option.)

PSMA PET can identify tumour recurrence even at low PSA values. Accordingly, its increasing use might necessitate a modification of the Phoenix definition of BCR after definitive RT to incorporate lower PSA cut-off values. This could be especially relevant for patients at an increased risk of recurrence, such as those classified as having a high risk and for patients who are theoretically fit for local salvage therapy options [128].

**Q59.** When asked at what confirmed PSA level, they recommend imaging for asymptomatic patients with rising PSA after radical (definitive) RT of the prostate with interval to biochemical failure <18 mo or biopsy ISUP grade group 4–5 (*EAU high-risk category*), 54% of panellists voted for ≥2 ng/ml above nadir, 38% voted for imaging before PSA reaches <2 ng/ml above nadir, and 8% voted for ≥2 ng/ml above nadir and PSA-DT <12 mo. There were four abstentions. (No consensus for any given answer option.)

**Q60.** As a first step for imaging in patients with rising PSA after RT therapy of the prostate with interval to biochemical failure <18 mo or biopsy ISUP grade group 4–5 (*EAU high-risk category*), 84% of panellists voted for PSMA PET, 10% voted for CT and/or bone scintigraphy, 5% voted for MRI of the pelvis alone, and 1% voted for whole-body MRI alone/choline/fluciclovine PET/CT. There were two abstentions. (Consensus for PSMA PET.)

Given the morbidity of local salvage options, it is appropriate that patients with local recurrence after RT first have a histological confirmation [6]. As mentioned, various rescue treatments are available after definitive RT; these have shown no differences in efficacy but meaningful differences in toxicity [127]. For example, genitourinary toxicity was found to exceed 21% for HIFU and RP, whereas it ranged from 4.2% to 8.1% with reirradiation. Rates of severe gastrointestinal toxicity also are reportedly lower with reirradiation, particularly with HDR brachytherapy [127]. In some circumstances, ADT can be used instead of these salvage treatments [5,6]. However, there is no evidence supporting the use of ADT in patients who are candidates for reirradiation [129].

**Q61.** For patients with suspected local recurrence based on prostate imaging after radical local RT, 67% of panellists voted to recommend biopsy only if local salvage therapy is planned, 20% voted for biopsy in the majority of patients, and 13% voted against biopsy. There were four abstentions. (No consensus for any given answer option; a combined total of 87% voted for a biopsy at least in selected patients.)

**Q62.** For patients with a *confirmed local recurrence in the prostate after radical local RT* with interval to biochemical failure <18 mo or biopsy ISUP grade group 4–5 (EAU high risk), who are suitable for a second definitive treatment and without detectable metastases, 29% of panellists voted for salvage prostatectomy, 20% voted for HIFU and/or cryotherapy and/or IRE, 16% voted for brachytherapy, 14% voted for EBRT reirradiation with or without brachytherapy, and 21% voted that they do not recommend a second definitive local treatment option in this situation. There were 14 abstentions. (No consensus for any given answer option.)

**Q63.** Among panellists who voted for reirradiation in Q62, 48% voted to combine it with short-term (eg, 6 mo) systemic hormonal therapy, 36% voted to combine it with long-term (eg, 2–3 yr) systemic hormonal therapy, and 16% voted not to combine it with systemic hormonal therapy (ie, reirradiation alone). There were 74 abstentions (including those who did not recommend reirradiation in this setting). (No consensus for any given answer option; a combined total of 84% voted for systemic hormonal therapy.)

There is no high-level evidence on how best to treat patients with confirmed local recurrence in the prostate bed after RP and sRT. Other local treatments could be discussed if these are feasible. Alternatively, for high-risk patients (PSA-DT ≤12 mo and/or ISUP grade group ≥4), the initiation of systemic hormonal therapy could be considered.

**Q64.** For patients with a *confirmed local recurrence in the prostate bed* after RP and local sRT, if imaging shows no evidence of distant metastases, 54% of panellists voted not to recommend another local treatment, 24% voted for EBRT reirradiation or SBRT, 11% voted for HIFU and/or cryotherapy, 7% voted for salvage selective resection, and 4% voted for brachytherapy. There were 14 abstentions. (No consensus for any given answer option.)

**Q65.** For patients with *rising PSA after definitive local therapy (RP with or without sRT, or RT of the prostate)* in a lower-risk setting (PSA-DT ≥12 mo and/or ISUP grade group ≤3), if there are *no options for local salvage therapy* and no detectable metastases on imaging, 89% of panellists voted for monitoring PSA and imaging until detection of metastases, and 11% voted for starting immediate systemic therapy for the majority of patients. There were five abstentions. (Consensus to monitor until detection of metastases.)

**Q66.** For patients with *rising PSA after definitive local therapy (RP with or without sRT, or RT of the prostate)* in a higher-risk setting (PSA-DT <12 mo and/or ISUP grade group 4–5), if *there are no options for local salvage therapy* and no detectable metastases on imaging, 67% of patients voted for starting immediate systemic therapy for the majority of patients, and 33% voted for monitoring PSA and imaging until detection of metastases. There were three abstentions. (No consensus for any given answer option.)

For patients with recurrence of pelvic nodal disease after definitive RT, the initiation of ADT should be considered unless the priority is to delay systemic treatment. The use of MDT in combination with ADT may also be considered [130]. In light of recent results from the STAMPEDE trial, the possibility of 2 yr of abiraterone plus ADT and RT (if indicated) is another option [50].

**Q67.** For patients with rising PSA after radical local RT of the prostate and pelvis, if there are *one to three positive lymph nodes in the pelvis on conventional imaging* that on PSMA PET imaging are *located only inside the previous radiation treatment portal*, 43% of panellists voted to recommend

systemic therapy alone, 38% voted for locoregional treatment plus systemic therapy, 10% voted for monitoring alone, and 9% voted for locoregional treatment alone. There were nine abstentions. (No consensus for any given answer option, but combined 81% voted for systemic therapy ± locoregional treatment.)

**Q68.** Among those panellists who voted for locoregional treatment alone or systemic therapy in Q67, 56% voted for RT, 42% voted for surgery, and 2% voted for another form of locoregional treatment (eg, HIFU). There were 60 abstentions, including those who did not vote for locoregional treatment. (No consensus for any given answer option.)

**Q69.** For patients with rising PSA after radical local radiation of the prostate alone (no pelvic RT) and *one to three positive lymph nodes in the pelvis alone* on PSMA PET, 75% of panellists voted for locoregional treatment plus systemic therapy, 19% voted for locoregional treatment alone, and 6% voted for systemic therapy alone. There were seven abstentions. (Consensus for loco-regional treatment plus systemic therapy.)

**Q70.** Among those panellists who voted for locoregional treatment in Q69, 82% voted to recommend RT and 18% voted for surgery. There were 15 abstentions, including those who did not vote for locoregional treatment. (Consensus for RT among the panellists who voted for locoregional treatment.)

In patients with rising PSA after RP and a local relapse detected by MRI and/or PSMA PET, a boost to the lesion in addition to sRT plus ADT could help achieve better local disease control. However, we currently have no evidence that this is so.

**Q71.** For patients with rising PSA and a *local relapse detected by MRI and/or PSMA PET after RP* who had no prior history of local sRT, 68% of panellists voted for treatment with RT (EBRT with or without boost to the lesion or SBRT) *plus* systemic therapy, 29% voted for RT of the prostatic bed with or without boost to the lesion, and 3% voted for SBRT of the lesion alone. There were six abstentions. (No consensus for any given answer option, no one voted for systemic therapy alone.)

### 3.1. Discussion of part 2: PSA persistence and BCR

For patients with PSA persistence after RP, panellists reached strong consensus in favour of PSMA PET imaging, despite sparse prospective data supporting this approach and limited evidence that it affects survival outcomes. When PSMA PET is negative in patients with PSA persistence after RP, there was consensus to treat with sRT and systemic hormonal therapy if risk factors are present (Table 2).

Patients with BCR and negative PSMA PET who meet EAU low-risk criteria generally have more favourable outcomes, and there is only limited evidence that immediate treatment improves these outcomes. For this reason, current guidelines list monitoring without immediate treatment as an option. Most panellists, however, voted for some form of active treatment in this setting; only 28% voted for monitoring without immediate treatment in case of negative PSMA PET and 20% voted for monitoring in case PSMA PET was not available. Only 6% of panellists voted not to recommend imaging in this setting.

For patients with BCR who meet EAU high-risk criteria, there was consensus for PSMA PET imaging at a confirmed PSA level of >0.2–0.5 ng/ml. About half of panellists voted that they would wait until PSA >0.2 ng/ml and then use PSMA PET to guide salvage treatment, while the other half would perform sRT as early as possible, without waiting for patients to reach a PSA threshold. Indeed, a combined total of 81% of panellists voted in favour of offering sRT with or without systemic therapy when PSMA PET is negative in EAU high-risk patients with BCR. Interestingly, panellists rarely voted for systemic treatment alone as a noncurative treatment option for patients with BCR. Some panellists seem to tend to wait to offer some form of therapy in this setting until PSMA PET is positive, therefore delaying sRT even though there are no data to support such an approach.

The question of whether to add systemic therapy to sRT and how to select the best candidates for it remains a matter of debate. The panel voted on PSA cut-offs (<0.7 vs ≥0.7 ng/ml) and their preferred management strategies. For patients with BCR and pre-RT PSA <0.7 ng/ml, a combined total of 77% of panellists voted for sRT with systemic therapy (61% voted for 6 mo of systemic therapy, while 16% voted for 24 mo). For patients with BCR and pre-RT PSA ≥0.7 ng/ml, a combined total of 91% of panellists voted for sRT with systemic therapy (6 mo: 63%; 24 mo: 28%). For patients with PSA ≥0.7 ng/ml, a minority of panellists (<10%) voted for using a genomic classifier to help guide the decision about whether to start systemic therapy. The preferred form of hormonal treatment was LHRH analogues, but interestingly, there was no consensus on how to manage this relatively common scenario or what factors would influence treatment choice. Of note, the results of the RADICALS-HD trial and the DADSPORT meta-analysis were presented after APCCC 2022 at ESMO 2022. There was consensus not to use genomic classifiers routinely to guide treatment decisions in patients with BCR. There also was consensus to treat with both RT and systemic hormonal therapy when patients have PSMA-positive findings only in the pelvis.

The topic of BCR after radical RT was also controversial, finding consensus only for PSMA PET as the preferred imaging modality. For patients meeting EAU high-risk criteria, 38% of panellists voted to perform imaging before PSA reaches the traditional threshold for BCR after radical RT (≥2 ng/ml above nadir). Panellists did not reach consensus on most questions regarding preferred treatment, reflecting a lack of relevant robust data. In all, 30% voted for reirradiation and 29% voted for salvage prostatectomy. However, when deciding on local treatment of a suspected local relapse, a majority of panellists voted to first confirm the findings with biopsy. In addition, for patients receiving reirradiation of a local recurrence in the prostate, a combined total of 84% of panellists voted to add systemic hormonal therapy to RT (6 mo: 48%; 2–3 yr: 36%). For patients who have received definitive local therapy (RP with or without sRT or RT of the prostate) and then experience a rise in PSA (doubling time ≥12 mo and ISUP 1–3 disease), if there is no option for local salvage therapy and no metastases are

**Table 2 – APCCC 2022 questions concerning PSA persistence and biochemical recurrence after definitive treatment that have reached a consensus**

| Question | Answers | Voting results, % (*n*) |
|---|---|---|
| 34. In the majority of patients with PSA persistence 4–8 wk after radical prostatectomy (pN0) and M0 on preoperative imaging, do you recommend PSMA PET? | 1. Yes | 91 (90), strong consensus |
| | 2. No | 9 (9) |
| 36. What do you recommend for a patient with PSA persistence 4–8 wk after radical prostatectomy (pN0 and ≥2 risk factors: R1, pT3, ISUP grade group 4–5), M0 on preoperative imaging, and negative postoperative PSMA PET, provided that the patient has regained continence? | 1. Salvage radiation therapy | 10 (10) |
| | 2. Salvage radiation therapy plus systemic hormonal treatment | 77 (76), consensus |
| | 3. Systemic hormonal treatment alone | 1 (1) |
| | 4. No immediate active treatment, PSA surveillance | 12 (12) |
| 42. For the majority of patients with rising PSA after radical prostatectomy and PSA-DT <1 yr or pathological ISUP grade group 4–5 (EAU high risk), at what confirmed rising PSA level do you recommend PSMA PET imaging? | 1. PSA below 0.2 ng/ml | 11 (11) |
| | 2. PSA >0.2–0.5 ng/ml | 80 (78), consensus |
| | 3. PSA >0.5 ng/ml | 9 (9) |
| | 4. No imaging | 0 (0) |
| 44. For the majority of patients with rapidly rising PSA (eg, PSA-DT <3 mo) after radical prostatectomy (ISUP grade group 4–5 and/or pT3/4) with negative PSMA PET or no PSMA PET imaging available, what is your management recommendation? | 1. Active monitoring and treat only in case of a positive lesion on follow-up imaging | 8 (8) |
| | 2. Salvage RT alone | 6 (6) |
| | 3. Salvage RT plus systemic therapy | 75 (75), consensus |
| | 4. Systemic therapy alone | 11 (11) |
| 49. In the majority of patients with a PSA rise after radical prostatectomy (±salvage RT of the prostate bed) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your treatment recommendation? | 1. Locoregional treatment alone | 10 (10) |
| | 2. Systemic therapy alone | 5 (5) |
| | 3. Locoregional treatment plus systemic therapy | 85 (84), consensus |
| 50. If you voted for locoregional treatment in the previous question in the majority of patients with a PSA rise after radical prostatectomy (±salvage RT of the prostate bed) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your preferred strategy? | 1. Radiation therapy | 92 (85), strong consensus |
| | 2. Surgery | 8 (7) |
| 51. Outside of clinical trials, do you recommend the use of a molecular classifier (eg, Decipher) for patients with undetectable postoperative PSA after radical prostatectomy but subsequently rising PSA? | 1. Yes | 18 (17) |
| | 2. No | 82 (78), consensus |
| 52. Outside of clinical trials, do you recommend the use of a molecular classifier (eg, Decipher) for patients with PSA persistence (never achieved undetectable postoperative PSA) after radical prostatectomy? | 1. Yes | 20 (19) |
| | 2. No | 80 (75), consensus |
| 54. If you recommend systemic therapy in combination with salvage radiation therapy in the majority of patients with rising PSA after radical prostatectomy and negative PSMA PET, what do you recommend? | 1. ADT (LHRH agonist or antagonist) | 85 (80), consensus |
| | 2. ADT plus AR pathway inhibitor | 10 (9) |
| | 3. Bicalutamide monotherapy | 5 (5) |
| 55. If you recommend systemic hormonal treatment in combination with salvage radiation therapy in the majority of patients with rising PSA after radical prostatectomy and negative PSMA PET, which duration of AR blockade do you recommend for the majority of patients? | 1. Short term (eg, 6 mo) | 80 (76), consensus |
| | 2. Long term (eg, 18–24 mo) | 20 (19) |
| 57. Which imaging modality do you recommend as a first imaging step for patients with rising PSA after radical radiation therapy of the prostate with an interval to biochemical failure of >18 mo and biopsy ISUP grade group <4 (EAU low risk), assuming that all imaging modalities are available? | 1. MRI of the pelvis alone | 11 (12) |
| | 2. CT and/or bone scintigraphy | 9 (9) |
| | 3. Whole-body MRI alone/choline/fluciclovine PET/CT | 1 (1) |
| | 4. PSMA PET | 78 (80), consensus |
| | 5. I do not recommend imaging in this situation | 1 (1) |
| 60. Which imaging modality do you recommend as a first imaging step for patients with rising PSA after radical radiation therapy of the prostate with an interval to biochemical failure of <18 mo or biopsy ISUP grade group 4–5 (EAU high risk), assuming that all imaging modalities are available? | 1. MRI of the pelvis alone | 5 (5) |
| | 2. CT and/or bone scintigraphy | 10 (10) |
| | 3. Whole-body MRI alone/choline/fluciclovine PET | 1 (1) |
| | 4. PSMA PET | 84 (87), consensus |
| | 5. I do not recommend imaging in this situation | 0 (0) |

(*continued on next page*)

**Table 2 (*continued*)**

| Question | Answers | Voting results, % (*n*) |
|---|---|---|
| 65. What do you recommend in patients with rising PSA after definitive local therapy (RP ± salvage RT, RT of the prostate), with no local salvage therapy options available and no detectable metastases on imaging, and in a lower-risk setting (PSA-DT ≥12 mo and/or ISUP grade group ≤3)? | 1. Start immediate systemic therapy for the majority of patients | 11 (11) |
| | 2. Monitor by PSA and imaging until detection of metastases | 89 (89), consensus |
| 69. In the majority of patients with PSA rise after radical local radiation of the prostate alone (no pelvic RT) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your treatment recommendation? | 1. Locoregional treatment alone | 19 (19) |
| | 2. Systemic therapy alone | 6 (6) |
| | 3. Locoregional treatment plus systemic therapy | 75 (73), consensus |
| 70. If you voted for locoregional treatment in the majority of patients with PSA rise after radical local radiation of the prostate alone (no pelvic RT) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your preferred strategy? | 1. Radiation therapy | 82 (74), consensus |
| | 2. Surgery | 18 (16) |

ADT = androgen deprivation therapy; APCCC = Advanced Prostate Cancer Consensus Conference; AR = androgen receptor; CT = computed tomography; EAU = European Association of Urology; ISUP = International Society of Urological Pathology; LHRH = luteinising hormone-releasing hormone; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; RT = radiation therapy.

detected on imaging, there was consensus in favour of monitoring, with only 11% of panellists voting for immediate systemic therapy. For patients with the same characteristics but PSA-DT ≤12 mo and/or ISUP 4–5 disease, 67% of panellists voted in favour of immediate systemic therapy. For patients with a limited number of positive lymph nodes in the pelvis on PSMA PET after prior RT of the prostate alone, there was a consensus for locoregional treatment plus systemic therapy.

In summary, PSMA PET has become a preferred imaging modality for patients with PSA persistence and BCR, but the management of these common and heterogeneous situations remains challenging. Large trials of specific populations or at least subgroups with prognostic stratification factors are needed. Several relevant trials are on-going (ie, INDICATE NCT04423211 and PRESTO NCT04115007) and will hopefully lead to improved understanding. Many patients with BCR may not need treatment; thus, it will be important to obtain robust data to build on when making treatment decisions. It appears that for patients with BCR, some panellists tend to delay treatment, including sRT, until PSMA PET is positive, even though there are no data to support this approach. Specifically for patients with rapid PSA-DT and/or other adverse factors, it is questionable whether it is optimal to wait for starting treatment until lesions appear on serial PSMA PET scans. More trials in this setting are needed urgently. Available data on genomic classifiers, namely Decipher, also raise questions as to the added value of such tests beyond already existing and more readily accessible clinicopathological data. Again, prospective validation trials are needed.

## 4. Management of side effects caused by hormonal therapy

Cardiovascular events are a significant cause of death in patients with advanced prostate cancer [131]. Many factors may contribute to the increased risk for cardiovascular events in patients with advanced prostate cancer who are receiving systemic therapies [132,133]. The novel potent ARPIs (abiraterone, apalutamide, darolutamide, and enzalutamide) have been associated with a small increase in cardiovascular events in clinical trials, but this could partly be due to longer time on trial and capturing of events related to increasing age [134–136]. Alterations in body composition, lipid profile abnormalities, and impaired glucose control have been discussed as potential underlying mechanisms [1–3]. For the combination of apalutamide plus ADT, an increase in triglycerides and cholesterol was documented in the TITAN trial, in which patients in the control arm received ADT alone [137]. In the HERO trial, which compared the oral LHRH antagonist relugolix with the LHRH agonist leuprorelin, the risk for major adverse cardiovascular events (MACEs) with LHRH agonists was most pronounced in patients with a history of prior MACEs [138]. APCCC 2022 panellists discussed questions about performing a cardiovascular assessment before starting systemic therapy and monitoring of patients on ARPIs (see Table 3 and supplement 3 for details).

**Q122.** Before starting patients with mHSPC on hormonal therapy, 28% of panellists recommended obtaining a baseline electrocardiogram (ECG) in the majority of patients, 44% recommended doing so only if there is a history of a MACE or other risk factors for cardiac disease, and 28% voted against a baseline ECG. There were five abstentions. (No consensus for any given answer option.)

**Q123.** For patients with mHSPC, before starting an ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide) plus ADT, 14% of panellists voted to recommend a *cardiac evaluation* (including, eg, echocardiography) in the majority of patients, 57% voted for cardiac evaluation only if patients have a history of MACE(s), and 29% voted against it. There were five abstentions. (No consensus for any given answer option.)

**Q124.** For patients on an ARPI, 17% of panellists voted to recommend monitoring lipid profiles at baseline, 59% voted to recommend doing so at baseline and then regularly thereafter (eg, every 6–12 mo), and 24% voted against lipid monitoring. There were four abstentions. (No consensus for

any given answer option, but combined 76% voted for some form of lipid monitoring.)

Polypharmacy for age-related comorbidities is common among patients with advanced prostate cancer and increases the potential for drug-drug interactions (DDIs). A relevant number of DDIs are known, particularly for enzalutamide and apalutamide, and to a lesser extent for darolutamide [139]. Abiraterone also has several known DDIs [140]. Novel anticoagulants, statins, antihypertensives, and antibiotics are the most relevant drugs associated with DDIs when treating prostate cancer; when patients are receiving these drugs, it is especially important to consult prescribing information or online DDI tools [141].

**Q125.** In all, 95% of panellists voted to recommend checking for DDIs (either themselves or by consulting a pharmacist) before starting an ARPI plus ADT in patients with mHSPC, while 5% voted against this recommendation. There were six abstentions. (Strong consensus to check for DDIs before starting an ARPI.)

**Q126.** In all, 91% of panellists voted to recommend checking for DDIs (themselves or by consulting a pharmacist) before commencing other drugs in patients on an ARPI, while 9% of panellists voted against this recommendation. There were five abstentions. (Strong consensus to check for DDIs before starting other drugs in patients on an ARPI.)

Lower urinary tract symptoms are common in patients with advanced prostate cancer, and there is evidence that LHRH antagonists may be superior for improving these symptoms compared with LHRH agonists [142]. In benign prostate hyperplasia tissue, the high rate of LHRH receptor expression may explain the above-mentioned observation [143].

**Q127.** For patients with mHSPC with *severe voiding symptoms*, the panel voted on their preferred type of ADT when starting this treatment: 64% of panellists voted for LHRH antagonist, 33% voted for starting with LHRH with initial flare protection (with any kind of ARPI), and 3% voted for orchiectomy. There were five abstentions. (No consensus for any given answer option.)

Bone health has been discussed at prior APCCCs [1–3]. In 2022, panellists voted on questions related to bone health agents in mHSPC. Since the most recent APCCC (held in 2019), the ESMO has released new guidelines [144]. For patients with cancer who are receiving chronic endocrine therapy that is known to accelerate bone loss (ADT in the case of prostate cancer), in addition to basic measures (calcium and vitamin D3 supplementation, exercise, smoking cessation, and no or low alcohol consumption), a risk-adapted approach is recommended that incorporates the following risk factors: T score <–1.5, smoking (current and historical), body mass index <24, family history of hip fracture, personal history of fragility fracture at >50 yr of age, and oral glucocorticoid use for >6 mo [144]. Patients with a T score of ≥–2.0 and no additional risk factors can undergo observation, with bone mineral density (BMD) reassessed in 1–2 yr, while patients who have two or more of the above risk factors or a T score of <–2 are recommended to start denosumab or a bisphosphonate at the dose and schedule used for osteopenia/osteoporosis [144]. Web-based tools such as the Fracture Risk Assessment Tool (FRAX) currently do not integrate cancer treatment–induced bone loss but can still help clinicians evaluate risk factors for fracture and calculate individual fracture risk.

**Q128.** For patients with *mHSPC starting on ADT*, 10% of panellists voted that they routinely recommend initiating denosumab or a bisphosphonate at the dose and schedule used for the prevention of cancer treatment–induced bone loss, 71% voted for doing so only in select patients as guided by risk assessment (eg, according to the FRAX score, ESMO guidelines, or BMD), and 19% voted that they do not recommend this. There were six abstentions. (No consensus for any given answer option; a combined 81% voted for osteoprotection at least in selected patients.)

**Q129.** When recommending denosumab or a bisphosphonate for patients with mHSPC, 75% of panellists voted to recommend administering denosumab every 6 mo or bisphosphonates orally or intravenously (i.v.) every 12 mo, 5% voted for denosumab 120 mg every 4 wk or zoledronic acid every 3–4 wk, and 20% voted that they do not recommend these drugs for patients with mHSPC. There were eight abstentions. (Consensus for denosumab every 6 mo or bisphosphonates orally or i.v. every 12 mo.)

**Q130.** For patients with mHSPC starting on ADT *plus an ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide)*, 19% of panellists voted that they routinely recommend initiating denosumab or a bisphosphonate at the dose and schedule used for the prevention of cancer treatment–induced bone loss in the majority of patients, 63% voted for doing so only in select patients as guided by risk assessment (eg, according to the FRAX score, ESMO guidelines, or BMD), and 18% voted against doing so. There were eight abstentions. (No consensus for any given answer option; a combined 82% voted for osteoprotection at least in selected patients.)

Severe vertebral fractures have been reported in postmenopausal patients who stop denosumab after receiving it for osteoporosis prevention [145]. In addition, a report documented similar findings in two men who had received denosumab for the same indication [146]. To help avert this risk, a consolidating dose of a bisphosphonate has been suggested for patients stopping denosumab [147,148].

**Q131.** For patients on long-term denosumab (twice per year) who have to stop treatment with denosumab, 33% of panellists voted in favour and 67% voted against recommending a consolidating dose of zoledronic acid to prevent rebound bone loss. There were 26 abstentions (including panellists who did not recommend denosumab in this setting). (No consensus for any given answer option.)

Osteonecrosis of the jaw (ONJ) is a well-recognised adverse event of denosumab and bisphosphonate therapy. Risk increases with cumulative dose. Consequently, the rate of ONJ in patients receiving the dose and schedule recommended to prevent cancer treatment–induced bone loss or osteoporosis is very low (<1%) [149]. Risk factors for ONJ include smoking, older age, ill-fitting dentures, poor dental hygiene, invasive dental procedures, concomitant therapy with antiangiogenic drugs, corticosteroid therapy, and RT in the head and neck area [150].

**Q132.** In all, 92% of panellists voted for and 8% voted against performing dental check before starting osteoclast-

targeted therapy in patients with mHSPC. There were seven abstentions. (Strong consensus to perform a dental check before starting osteoclast-targeted therapy.)

### 4.1. Discussion of part 3: management of side effects caused by hormonal therapy

Long-term side effects of hormonal treatments are often underestimated. In recent years, survival among patients with advanced and metastatic prostate cancer has increased significantly, which has increased durations of exposure to hormonal therapies. This makes their side effects increasingly important (Table 3).

Interestingly, only a minority of panellists voted that they would perform either an ECG or a more intensive cardiac evaluation before starting hormonal therapy for the majority of patients, despite the known association between hormonal therapies and MACEs and the fact that, at least for the newer hormonal treatments, pivotal trials included fairly strict cardiac eligibility criteria. Although more panellists would perform a cardiac workup for patients who have a history of MACEs, approximately 30% voted that they do not perform these investigations at all, which is surprising considering that an ECG is a rather easy and inexpensive test, and all the available ARPIs are associated with a known risk of QTc prolongation.

In contrast, there was strong consensus to check for potential DDIs before starting any ARPI. This is crucial because hormonal therapies can interact with a variety of common drugs and drug classes that older patients are especially likely to be prescribed for comorbidities.

When asked about starting bone-targeted agents at the dose and schedule recommended to prevent osteoporosis, only approximately 20% of panellists voted against doing so for patients with mHSPC who initiate systemic therapy, while the majority voted to prescribe them for selected patients who are at a higher risk of fracture. When starting a bone-targeted agent, there was consensus to first ensure that patients receive a dental check.

In conclusion, the voting results suggest that even among experts, there is no consensus about which routine evaluations for cardiologic/metabolic diseases to perform in patients with advanced prostate cancer. This could be because such evaluations are often performed by general practitioners/primary care providers. Nonetheless, both clinicians and patients need to be fully informed about the side-effect profiles of treatments used for advanced prostate cancer, what signs and symptoms to watch for, and whom to contact if these are observed. Communication between prostate cancer specialists and general practitioners is crucial. We should take time to inform our colleagues about potential side effects and make sure that they understand that some of our newer oral drugs may interact with other medications that they may prescribe.

## 5. Conclusions

APCCC provides a unique opportunity to gather the opinions of recognised prostate cancer experts who meet to discuss and vote on open questions that are not fully addressed by the existing literature and therefore remain topics with weak evidence, including in guidelines. APCCC also identifies priority areas where research should focus to help fill critical gaps in knowledge [151]. In a field that is rapidly changing, such as the management of locally advanced and biochemically recurrent prostate cancer, it is important to recognise that the voting at APCCC reflects what experts currently think based on their experience and knowledge of the literature and existing evidence. For the majority of questions, it was assumed that all diagnostic and therapeutic options were available without restrictions. However, experts with little or no experience with newer tests and modalities, such as next-generation imaging or genomic classifiers, may hesitate to vote for answers that include such options. As mentioned in our report of the APCCC 2019, expert opinion statements may be criticised, which remains a limitation of a consensus approach [3,152]. APCCC has worked to address these issues by considerably expanding the number of voting panel members from 61 experts in 2019 to >105 experts in 2022.

**Table 3 – APCCC 2022 questions concerning importance of lifestyle and prevention of side effects caused by hormonal therapy that have reached consensus**

| Question | Answers | Voting results, % (*n*) |
|---|---|---|
| 125. Do you recommend checking drug-drug interaction (yourself or by a pharmacist) in patients with mHSPC before the start of an AR pathway inhibitor (Abi/Apa/Daro/Enza) in addition to ADT? | 1. Yes | 95 (93), strong consensus |
| | 2. No | 5 (5) |
| 126. Do you recommend checking for drug-drug interactions (yourself or by a pharmacist) if other drugs are commenced after a patient has started an AR pathway inhibitor? | 1. Yes | 91 (90), strong consensus |
| | 2. No | 9 (9) |
| 129. In the majority of patients with mHSPC for whom you recommend initiating denosumab or a bisphosphonate, which dose and schedule do you use? | 1. Denosumab (q6 mo) or bisphosphonates (oral or q12 mo) | 75 (72), consensus |
| | 2. Denosumab 120 mg q4 wk or zoledronic acid q3–4 wk | 5 (5) |
| | 3. I do not recommend these drugs in mHSPC | 20 (19) |
| 132. In the majority of patients with mHSPC for whom you recommend an osteoclast-targeted therapy, do you recommend a dental check before initiation of treatment? | 1. Yes | 92 (89), strong consensus |
| | 2. No | 8 (8) |

Abi = abiraterone; ADT = androgen deprivation therapy; Apa = apalutamide; APCCC = Advanced Prostate Cancer Consensus Conference; AR = androgen receptor; Daro = darolutamide; Enza = enzalutamide; mHSPC = metastatic hormone-sensitive prostate cancer.

Finally, although this report captures what experts in the field think today, it should be interpreted and integrated into clinical practice with the same scrutiny that any other major paper would receive, and with the knowledge that consensus does not constitute or substitute for evidence.

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