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Original Article

Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC)

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Abstract

Background and objective: Innovations have improved outcomes in advanced prostate cancer (PC). Nonetheless, we continue to lack high-level evidence on a variety of topics that greatly impact daily practice. The 2024 Advanced Prostate Cancer Consensus Conference (APCCC) surveyed experts on key questions in clinical management in order to supplement evidence-based guidelines. Here we present voting results for questions from APCCC 2024.

Methods: Before the conference, a panel of 120 international PC experts used a modified Delphi process to develop 183 multiple-choice consensus questions on eight different topics. Before the conference, these questions were administered via a web-based survey to the voting panel members (“panellists”).

Key findings and limitations: Consensus was a priori defined as ≥75% agreement, with strong consensus defined as ≥90% agreement. The voting results show varying degrees of consensus, as discussed in this article and detailed in the Supplementary material. These findings do not include a formal literature review or meta-analysis.

Conclusions and clinical implications: The voting results 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 in prioritising areas for future research. Diagnostic and treatment decisions should always be individualised on the basis of patient and cancer characteristics, and should incorporate current and emerging clinical evidence, guidelines, and logistic and economic factors. Enrolment in clinical trials is always strongly encouraged. Importantly, APCCC 2024 once again identified important gaps (areas of nonconsensus) that merit evaluation in specifically designed trials.

ADVANCING PRACTICE

What does this study add?
Although scientific progress has contributed to improvements in outcomes for patients with advanced prostate cancer, there are still a variety of topics that greatly impact daily practice for which high-level evidence is lacking. The results from APCCC 2024 can help physicians and patients navigate controversial areas of clinical management for which there is no high-level evidence or the data are conflicting. APCCC 2024 identified important gaps (areas of nonconsensus) that merit evaluation in specifically designed trials.

Clinical Relevance
The 2024 Advanced Prostate Cancer Consensus Conference showcases notable progress in prostate cancer management while addressing areas where high-quality evidence remains limited. Through expert consensus voting, this report offers valuable insights into contentious clinical issues of advanced prostate cancer, especially in cases where guidelines are sparse or conflicting. It emphasizes the need for personalized treatment approaches that account for patient characteristics, evolving clinical data, and available resources. Additionally, it advocates for ongoing participation in clinical trials to bridge knowledge gaps. This comprehensive guide is designed to help physicians and patients make informed decisions, especially in complex cases. Associate Editor: Gianluca Giannarini MD.

Patient Summary
At the Advanced Prostate Cancer Consensus Conference, experts discuss current options for diagnosis and treatment of advanced prostate cancer (PC). The panel of experts vote on multiple-choice questions about their clinical opinions and approaches to management of advanced PC. This report presents the voting results for high-risk localised and locally advanced PC. The results provide a practical guide to help doctors and patients discuss treatment options as part of shared decision-making.

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1. Introduction

Despite recent progress in the management of advanced prostate cancer (PC), many clinical questions and controversies persist that directly impact daily practice. The Advanced Prostate Cancer Consensus Conference (APCCC) discussed these topics in detail, and physician experts then voted 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 for which high-level evidence is scant or conflicting.

Eight areas of clinical controversy in advanced PC were prioritised for discussion and consensus voting:

1. High-risk localised and locally advanced PC;
2. Prostate-specific antigen (PSA) persistence and biochemical recurrence (BCR);
3. Management of metastatic hormone-sensitive PC (mHSPC);
4. Management of metastatic castration-resistant PC (mCRPC);
5. Radioligand therapy (RLT) with ^{177}Lu-labelled prostate-specific membrane antigen (PSMA) ligands;
6. Management of side effects caused by hormonal therapy;
7. Bone protection in advanced PC; and
8. Genetics and genomics.

2. Materials and methods

Before APCCC 2024, a multidisciplinary panel of 120 international PC experts developed 183 multiple-choice consensus questions on these eight topics using the same modified Delphi process that was used at prior APCCCs and has been described previously [1–5]. Most panellists had helped to design consensus questions for previous APCCCs. Consensus voting at the APCCCs is performed by panel members, all of whom are physician experts who engage directly in clinical decision-making. In this paper, these voting panel members are referred to as "panellists." At APCCC 2024, the 106 voting panellists included medical oncologists (52%), urologists (27%), and clinical oncologists and radiation oncologists (21%). A total of 39% practice in Europe, 36% in North America, and 25% in other regions, including Australia, Asia, South America, the Middle East, and Africa (details at www.apccc.org). The 14 nonvoting panel members included experts in nuclear medicine, radiology, pathology, statistics, and health economics, a patient advocate, and one voting member who could not participate in the voting for personal reasons.

For all questions, unless stated otherwise, panellists were asked to assume that all diagnostic procedures and treatments were readily available, including the expertise in interpretation and application required, 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 PC was defined as positron emission tomography (PET)/computed tomography (CT), subsequently referred to as PET/CT (unless stated otherwise), with PSMA, choline, or fluciclovine tracers and/or whole-body morphological and diffusion-weighted magnetic resonance imaging (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 the percentage results, the number of abstainers was excluded from the denominator. Similar to 2022, consensus questions were administered via a web-based survey. The definitions used can be found in the Supplementary Document 1.

Levels of consensus were defined a priori as follows: ≥75% agreement on an answer option was defined as consensus, while ≥90% agreement on an answer option was defined as strong consensus, as used in prior APCCCs [4,5]. Here we present voting results for the 183 consensus questions. The Supplementary material contains detailed voting results for each question. For certain questions, we decided a priori to allow pooling of answer options with similar intent (eg, the answer options of radiation and radiation plus systemic therapy may be combined into a single answer option, radiation therapy intent).

3. Results

3.1. High-risk localised and locally advanced PC

3.1.1. General questions

Choice of treatment for localised PC is predicated on patient risk stratification, which is determined according to clinical staging, PSA, and Gleason score (GS) and International Society of Urological Pathology (ISUP) grade group (GG) [6,7]. The clinical Tumour Node Metastasis (TNM) classification is used to define clinical staging for patients with PC [6,7]. According to current international guidelines, the clinical tumour (cT) classification should be based on digital rectal examination (DRE) only and not on imaging, despite the well-established limitations of DRE [6,7]. DRE only allows the clinician to palpate the posterior part of the prostate gland; nonpalpable abnormalities can be characterised on multiparametric MRI (mpMRI) [8]. Despite the fact that DRE is highly subjective, most PC clinical trials have used it for defining cT stage, which then influences treatment recommendations. By contrast, enhanced technology such as prostate MRI may more accurately characterise the cT stage beyond DRE. According to European Association of Urology (EAU) guidelines, additional staging information derived from imaging should be reported separately [6]. It remains controversial whether DRE for staging can be replaced by MRI, as there are clear cost and accessibility considerations. Importantly, the panel did not address questions of early PC detection at APCCC 2024 but focused on high-risk localised and locally advanced PC.

At APCCC 2024, panellists voted on how to treat patients if there is a discordance between cT based on DRE and MRI.

Q1: In the majority of patients with localised prostate cancer and clinically T2 (DRE positive) cN0 cM0 and ISUP GG ≥3 carcinoma and clear evidence of T3 disease on MRI, what do you recommend?

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- Treat as T2: 4% (4 votes)
- Treat as T3: 96% (96 votes)
- Abstain/unqualified to answer (6 votes)

Strong consensus on recommending treatment as for T3 disease when there is clear evidence of T3 disease on MRI.

For many years, conventional imaging based on CT or abdominal/pelvic MRI and bone scintigraphy was used for staging in patients with high-risk PC. However, next-generation imaging techniques such as whole-body MRI and PSMA PET/CT have shown higher sensitivity and specificity in this setting [9–14]. It is important to note that PSMA PET alone is not sufficient for staging; a concurrent CT scan also needs to be interpreted and reported. For patients with high-risk disease, international guidelines classify PSMA PET/CT as a first-line staging tool owing to its greater sensitivity and specificity in comparison to conventional imaging [6,7]. Although PSMA is predominantly expressed in PC cells, it is also found in some benign cells and in other types of malignant tissue, leading to false-positive findings in some cases [15,16]. For example, ^{18}F-PSMA-1007 administration results in nonspecific accumulation in bone, which could be interpreted as bone metastases [16,17]. To minimise false positives, it is necessary to know which tracer was used and the intensity of PSMA uptake (mean and maximum) and the presence or absence of correlative findings in the CT component. The training and expertise of nuclear medicine physicians is key for these interpretations.

At APCCC 2022, 73% of the 105 voting panellists voted in favour of recommending additional imaging (eg, MRI, bone scintigraphy) in the majority of patients with PSMA-positive lesions in bone on PET without a correlate in the CT component [4]. Use of reporting guidelines such as PROMISE2 and E-PSMA may increase the reproducibility and clarity of PET reports [18,19]. Recognition of the normal biodistribution of PSMA and common pitfalls is also important [20]. At APCCC 2024, panellists were asked a similar question to gain an understanding of whether they would recommend further evaluation in such a situation or if they would "trust" the PSMA PET/CT result.

Q2: In the majority of patients with clinically high-risk localised or locally advanced prostate cancer and one PSMA PET positive bone lesion WITHOUT a correlate on the CT component of the initial PSMA PET, what do you recommend as next investigation?

- Correlative conventional imaging (eg, MRI, X-rays or bone scintigraphy): 55% (58 votes)
- Biopsy if feasible: 20% (21 votes)
- No further investigation, treat as M0: 13% (13 votes)
- No further investigation, treat as M1: 12% (13 votes)
- Abstain/unqualified to answer (including I do not recommend PSMA PET imaging in this situation) (1 vote)

No consensus.

A combined total of 75% voted for further investigation (additional imaging or biopsy).

3.1.2. Treatment of high-risk localised/locally advanced PC including cN1 disease

For patients with localised high-risk or locally advanced PC, international guidelines recommend radiotherapy (RT) to the prostate in combination with long-term (2–3 yr) androgen deprivation therapy (ADT) ± abiraterone acetate/prednisone (hereafter shortened to abiraterone) for 2 yr. Radical prostatectomy (RP) is another treatment option for selected patients as part of a multimodal treatment strategy [6,7].

The efficacy of abiraterone addition to RT + long-term ADT in this setting was demonstrated by results from an analysis of the STAMPEDE trial platform: addition of abiraterone (2 yr) to RT + ADT (3 yr) improved metastasis-free survival (MFS) and overall survival (OS) in comparison to RT + ADT (3 yr) [21]. Patients had either clinically node-positive disease (cN1 M0) or high-risk node-negative PC (defined as ≥2 of the following characteristics: ≥cT3, ISUP GG ≥4, and PSA ≥40 ng/ml). Of note, this high-risk definition differs from classical "high-risk" definitions such as those used in the National Comprehensive Cancer Network (NCCN) and EAU guidelines [6,7]. In STAMPEDE, conventional imaging including local MRI was used for staging, and RT was mandated for patients with node-negative disease and encouraged for patients with node-positive disease [21].

There are no data on whether addition of an androgen receptor pathway inhibitor (ARPI) other than abiraterone (such as apalutamide, darolutamide, or enzalutamide) can improve outcomes in patients with high-risk disease according to STAMPEDE criteria. Therefore, it is not known whether it is appropriate to substitute abiraterone with another ARPI in patients for whom abiraterone is not suitable.

Some guidelines recommend considering addition of docetaxel to RT and long-term ADT for patients with high-risk PC, although docetaxel has no proven OS benefit in this setting [22–24].

APCCC 2024 panellists voted on which treatment to recommend for patients with localised high-risk/locally advanced disease, and whether it is appropriate to replace abiraterone with another ARPI.

Q3: In the majority of patients with high-risk localised/locally advanced prostate cancer (STAMPEDE definition) N0 M0 on next-generation imaging, what is your recommended treatment?

- Radiation plus long-term ADT alone: 10% (11 votes)
- Radiation plus long-term ADT plus abiraterone for 2 years: 68% (72 votes)
- Radiation plus long-term ADT plus docetaxel: 0% (0 votes)
- Surgery, recognising that it may be part of a multimodality approach: 22% (23 votes)
- Abstain/unqualified to answer (0 votes)

No consensus.

A combined total of 78% voted for RT plus long-term ADT ± abiraterone.

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Q4: In the majority of patients with very high-risk localised prostate cancer (NCCN definition) and NOT high-risk localised/locally advanced prostate cancer (STAMPEDE definition) N0 M0 on next-generation imaging, what is your recommended treatment?

- Radiation plus long-term ADT alone: 29% (30 votes)
- Radiation plus long-term ADT plus abiraterone for 2 years: 55% (58 votes)
- Radiation plus long-term ADT plus docetaxel: 0% (0 votes)
- Surgery, recognising that it may be part of a multimodality approach: 16% (17 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

A combined total of 84% voted for RT plus long-term ADT ± abiraterone.

Q5: For patients with high-risk localised or locally advanced prostate cancer that you would like to treat with radiation therapy plus long-term ADT plus abiraterone for 2 years (M0 disease) and in case the patient is not eligible for abiraterone, is it appropriate to substitute abiraterone with one of the novel AR antagonists (Apa, Daro, Enza)?

- Yes: 74% (76 votes)
- No: 26% (27 votes)
- Abstain/unqualified to answer (including I do not use this regimen) (3 votes)

No consensus.

Q6: In general, is it appropriate for the majority of patients also if they are eligible for abiraterone to substitute abiraterone with one of the novel AR antagonists (Apa, Daro, Enza) in combination with radiation plus long-term ADT in M0 disease?

- Yes: 51% (53 votes)
- No: 49% (51 votes)
- Abstain/unqualified to answer (including I do not use this regimen) (2 votes)

No consensus.

Q7: In the majority of patients with high-risk localised/locally advanced prostate cancer cT3, Gleason 8–10 (no evidence of small cell carcinoma) and low PSA (eg, <3 ng/ml) what do you recommend?

- Radiation plus long-term ADT alone: 14% (15 votes)
- Radiation plus long-term ADT plus abiraterone for 2 years: 50% (52 votes)
- Radiation plus ADT plus 4–6 cycles of docetaxel: 4% (4 votes)
- Surgery, recognising that it may be part of a multimodality approach: 32% (34 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

Q10: In patients with high-risk localised/locally advanced prostate cancer that you treat with radiation therapy plus long-term ADT plus abiraterone for 2 years and with no relevant toxicity, is it appropriate to stop also the ADT after 2 years instead of after 3 years?

- Yes, in the majority of patients: 65% (68 votes)
- Yes, in selected patients (eg, with a relevant cardiovascular history): 30% (32 votes)
- No: 5% (5 votes)
- Abstain/unqualified to answer (including I do not use this regimen) (1 vote)

No consensus.

A combined total of 95% voted in favour of stopping ADT after 2 yr instead of after 3 yr, at least in selected patients.

Q11: For the majority of patients with high risk localised/locally advanced prostate cancer who are about to start ADT (± ARPI) do you recommend baseline testosterone measurement before starting systemic therapy?

- Yes: 75% (79 votes)
- No: 25% (27 votes)
- Abstain/unqualified to answer (0 votes)

Consensus in favour of recommending baseline testosterone measurement before starting systemic therapy.

Q20: What is your preferred treatment recommendation for the majority of patients with prostate cancer with newly diagnosed cN1 (pelvic lymph nodes) on conventional imaging and no distant lesions (M0)?

- Radiation therapy prostate plus pelvis plus long-term ADT: 4% (4 votes)
- Radiation therapy prostate plus pelvis plus long-term ADT plus abiraterone for 2 years: 92% (94 votes)
- Surgery, recognising that it may be part of a multimodality approach: 4% (4 votes)
- Abstain/unqualified to answer (4 votes)

Strong consensus in favour of RT (prostate plus pelvis) plus long-term ADT and abiraterone for 2 yr.

Q21: What is your preferred treatment recommendation for the majority of prostate cancer patients with cN0 on conventional imaging and positive pelvic lymph nodes on PSMA PET imaging but no distant lesions (M0) and otherwise NOT meeting the STAMPEDE (high-risk, locally advanced M0) definition?

- Radiation therapy prostate plus pelvis plus long-term ADT: 13% (13 votes)
- Radiation therapy prostate plus pelvis plus long-term ADT plus abiraterone for 2 years: 71% (73 votes)
- Surgery, recognising that it may be part of a multimodality approach: 16% (17 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

A combined total of 84% voted for RT to the prostate and pelvis plus long-term ADT ± abiraterone for 2 yr.

Q22: What is your preferred treatment recommendation for the majority of prostate cancer patients with cN0 on conventional imaging but positive pelvic lymph nodes

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on PSMA PET but no distant lesions (M0) and meeting also the STAMPEDE (high-risk, locally advanced M0) definition?

- Radiation therapy prostate plus pelvis plus long-term ADT: 5% (5 votes)
- Radiation therapy prostate plus pelvis plus long-term ADT plus abiraterone for 2 years: 86% (90 votes)
- Surgery, recognising that it may be part of a multimodality approach: 9% (9 votes)
- Abstain/unqualified to answer (2 votes)

Consensus in favour of recommending RT (prostate and pelvis) plus long-term ADT and abiraterone for 2 yr to patients with cN0 on conventional imaging but cN1 on PSMA PET and fulfilling the STAMPEDE high-risk cN0cM0 definition.

A meta-analysis of 12 randomised clinical trials of patients with localised PC treated with short-term ADT and prostate-only RT reported superior clinical outcomes after concurrent/adjuvant ADT in comparison to neoadjuvant/concurrent ADT [25,26]. Moreover, ADT sequencing exhibited a significant interaction with field size, with no differences observed among patients treated with whole-pelvis RT [27]. However, for patients with high-risk localised/locally advanced PC for whom RT and long-term ADT (± ARPI) is planned, there is no evidence of a detrimental effect of neoadjuvant systemic therapy, and this approach could be used in selected situations to reduce the local tumour burden before irradiation [28].

Both the EAU and NCCN guidelines strongly discourage the use of neoadjuvant ADT before RP [6,7]. All studies evaluating neoadjuvant ADT before surgery showed no benefit in terms of disease-free survival (DFS) or OS [29].

APCCC 2024 panellists voted on whether to recommend neoadjuvant hormonal treatment before RT or surgery.

Q8: In patients with high-risk localised/locally advanced prostate cancer planned for radiation therapy do you recommend neoadjuvant systemic therapy (3–9 months ADT ± ARPI) before starting radiation therapy?

- Yes, in the majority of patients: 46% (46 votes)
- Yes, in selected patients for downstaging or for logistical reasons (eg, long waiting time): 33% (33 votes)
- No: 21% (21 votes)
- Abstain/unqualified to answer (including I do not recommend radiation in this situation) (6 votes)

No consensus.

A combined total of 79% voted in favour of recommending neoadjuvant systemic therapy (3–9 mo of ADT ± ARPI) before the start of RT, at least in selected patients.

Q9: In patients with high-risk localised/locally advanced prostate cancer planned for radical prostatectomy do you recommend neoadjuvant systemic therapy (ADT ± ARPI) before surgery?

- Yes, in the majority of patients: 5% (5 votes)
- Yes, in selected patients for downstaging or for logistical reasons (eg, long waiting time): 15% (15 votes)
- No: 80% (80 votes)
- Abstain/unqualified to answer (including I do not recommend surgery in this situation): (6 votes)

Consensus against recommending neoadjuvant systemic therapy before RP.

3.1.3. Lymphadenectomy in localised PC

Extended pelvic lymph-node dissection (ePLND) includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located anteriorly and posteriorly to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. ePLND provides more complete staging and prognostic information [30,31]. Therefore, ePLND is preferred when PLND is performed. PLND can be excluded in patients with low nomogram-predicted risk of nodal metastases, although some patients with lymph node metastases will be missed [32–35]. There is no evidence-based threshold for performing PLND.

Despite better performance for staging and prognostication, there are currently no strong data to suggest that PLND provides a therapeutic benefit [31,36,37]. Furthermore, PLND is associated with relevant complications, the rate of which is higher for ePLND than for limited PLND (19.8% vs 8.2%) [38].

An update on the Limited versus Extended Lymph Node Dissection randomised clinical trial was presented at the EAU 2024 congress [39]. Initial results from this trial were published in 2021 and demonstrated that at median follow-up of ~3 yr, there was no significant difference in BCR rate between the ePLND and limited PLND groups [40]. Extended follow-up for this trial (4.2 yr) continues to demonstrate no significant benefit of ePLND in terms of BCR. However, the ePLND group had a lower incidence of metastases (hazard ratio [HR] 0.8; $p = 0.003$). According to the authors, one possible explanation for better MFS without a BCR benefit is the tumour self-seeding hypothesis, which postulates that metastases may spread from any site to another, for example, from the primary disease site to local lymph nodes or to distant metastases, and vice versa [39]. While interesting, the study results have not yet been peer-reviewed or published and are contentious, especially in light of the choice of BCR as the primary endpoint.

APCCC panellists voted on whether to recommend ePLND for patients with unfavourable intermediate-risk, high-risk, and very high-risk PC and negative PSMA PET/CT findings.

Q12: In patients with unfavourable intermediate-risk localised prostate cancer (NCCN definition) for whom radical prostatectomy is planned, and who have a negative PSMA PET (N0 M0), do you recommend an extended pelvic lymphadenectomy (ePLND)?

- Yes, in the majority of patients: 31% (27 votes)
- Yes, but only in selected patients: 25% (22 votes)
- No: 44% (38 votes)
- Abstain/unqualified to answer (19 votes)

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No consensus.

Q13: In patients with high-risk localised prostate cancer (NCCN definition) for whom radical prostatectomy is planned, and who have a negative PSMA PET (N0 M0), do you recommend an extended pelvic lymphadenectomy (ePLND)?

- Yes, in the majority of patients: 61% (54 votes)
- Yes, but only in selected patients: 10% (9 votes)
- No: 29% (25 votes)
- Abstain/unqualified to answer (18 votes)

No consensus.

Q14: In patients with very high-risk localised prostate cancer (NCCN definition) for whom radical prostatectomy is planned, and who have a negative PSMA PET (N0 M0), do you recommend an extended pelvic lymphadenectomy (ePLND)?

- Yes, in the majority of patients: 70% (61 votes)
- Yes, but only in selected patients: 8% (7 votes)
- No: 22% (19 votes)
- Abstain/unqualified to answer (19 votes)

No consensus.

A combined total of 78% voted in favour of recommending ePLND, at least in selected patients with very high-risk localised PC.

3.1.4. RT in high-risk localised and locally advanced PC

Local control is critical to RT outcomes in patients with PC; local failure because of an insufficient total RT dose is prognostic for death from PC [41]. Combination therapy with long-term ADT and dose-escalated RT (≥74 Gy) seems to be the best treatment strategy to optimise clinical outcomes in patients with localised PC, as shown by the HEAT network meta-analysis from the MARCAP consortium, which included 13 randomised clinical trials and more than 11 800 patients [42]. At the 2024 American Society of Clinical Oncology Genitourinary (ASCO GU) symposium, investigators reported long-term results from the randomised phase 3 GETUG-AFU 18 trial, which showed an OS benefit with dose-escalated RT (80 Gy, 2 Gy per fraction) versus conventional-dose RT (70 Gy) in patients with high-risk PC who were receiving long-term (3 yr) ADT [43].

Moderate RT hypofractionation (2.5–3.4 Gy per fraction) is an option for patients with high-risk PC and has the added advantage of being more convenient for patients and costing less [44,45]. In the phase 3 CHHiP trial, 12% of patients (n = 386) were at high risk, excluding patients with both T3a tumours and ISUP GG ≥4. Results were presented at ASCO GU 2023; at median follow-up of 12.1 yr, the 60-Gy hypofractionated schedule remained noninferior to 74-Gy conventional fractionation (rates of 10-yr biochemical failure [Phoenix consensus guidelines] or clinical failure were 79.8% vs 76%, and MFS rates were 94.3% vs 94%) [46]. Late bladder and gastrointestinal toxicities (6–10 yr after RT) were very infrequent in all treatment groups (1–2% of patients required transurethral resection of the prostate [TURP], urethrotomy, urethral dilation, or a long-term catheter, or developed a ureteric obstruction) [46].

The concept of dose escalation with delivery of a focal boost to the dominant intraprostatic lesion (DIL) visible on MRI was successfully validated in a randomised clinical trial in which more than 500 patients with high-risk PC received 77 Gy in 35 fractions of 2.2 Gy to the whole prostate gland, or the same dose plus a focal boost of up to 95 Gy to the DIL [47]. In the boost arm, there was a moderate improvement in biochemical progression–free survival (bPFS), a lower rate of local failure, and a higher MFS rate, without a significant difference in rates of late genitourinary and gastrointestinal toxicities [47]. A systematic review of MRI-defined DIL focal boost studies using standard fractionation showed good tolerability and better bPFS [48]. The role of MRI-defined DIL focal boost when using moderate hypofractionation or ultra-hyperfractionation is currently under investigation.

There is scarce evidence on ultra-hypofractionation (defined as RT delivering >6 Gy per fraction mostly using stereotactic body RT [SBRT] techniques) for high-risk/locally advanced PC, although its use in this setting is addressed in the NCCN PC guidelines [7,49,50]. In the HYPO-RT-PC randomised trial, 11% of patients had high-risk disease [50]. There was no difference in failure-free survival between conventional and ultra-hypofractionation, and no interaction between fractionation and risk class. The rate of acute grade ≥2 genitourinary toxicity was lower in the conventional fractionation arm (23% vs 28%), but there was no significant difference in long-term toxicity rates [50]. In a retrospective series that included 344 patients with high-risk PC treated with SBRT, the bPFS rate at 4 yr was 81.7%, although concomitant ADT was used in only 72% of the patients [51]. Rates of grade ≥3 genitourinary and gastrointestinal adverse events remained low (2.3% and 0.9%, respectively). Acute toxicity results from PACE-C, a phase 3 randomised clinical trial comparing SBRT with moderate hypofractionation in patients with unfavourable intermediate-risk and limited high-risk PC, with 6 mo of ADT in both arms, were presented at the 2024 European Society for Radiotherapy and Oncology (ESTRO) congress. SBRT resulted in slightly higher incidence of both acute genitourinary (28% vs 34%) and gastrointestinal (10% vs 17%) toxicity using Common Terminology Criteria for Adverse Events (CTCAE) grading, but differences were not detectable using the Radiation Therapy Oncology Group (RTOG) scale. There were no differences in the rate of grade ≥3 toxicity between the arms [52]. Similarly, acute toxicity results from the PRIME trial comparing moderate hypofractionation to SBRT in high-risk PC and node-positive PC were presented at ESTRO 2023. The rates of acute grade 2 genitourinary (33.1% vs 31.8%) and gastrointestinal (17.2% vs 15.2%) adverse events were similar between moderate hypofractionation and SBRT. Quality of life also was similar between the arms, as were rates of acute grade 3 toxicity (1% for genitourinary adverse events and 0.7% for gastrointestinal adverse events) [53].

At APCCC 2024, panellists voted on which RT fractionation and modality to use in patients with high-risk localised/locally advanced PC.

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Q15: In the majority of patients with high-risk localised/locally advanced prostate cancer undergoing radiation therapy to the prostate in combination with long-term ADT do you recommend a radiation therapy dose escalation (with an equivalent total dose of approximately 80Gy in 2Gy fractions)?

- Yes: 83% (63 votes)
- No: 17% (13 votes)
- Abstain/unqualified to answer (30 votes)

Consensus in favour of recommending RT dose escalation.

Q16: In the majority of patients with high-risk localised/locally advanced prostate cancer undergoing RT to the prostate, which dose escalation modality do you recommend?

- Combination of EBRT (45–50 Gy) + brachytherapy boost: 22% (14 votes)
- Whole prostate radiation therapy with standard fractionation (eg, 80 Gy in 40 fractions): 13% (8 votes)
- Whole prostate radiation therapy with moderate hypofractionation (eg, 62 Gy in 20 fractions equivalent to 80 Gy in 40 fractions): 46% (29 votes)
- Focal boost to the intraprostatic tumour (eg, 95 Gy in 35 fractions or 67 Gy in 20 fractions or equivalent): 19% (12 votes)
- Abstain/unqualified to answer (including I do not recommend dose escalation) (43 votes)

No consensus.

Q17: In the majority of patients with high-risk localised/locally advanced prostate cancer undergoing radiation therapy to the prostate, what fractionation do you recommend?

- Conventional (1.8–2 Gy/fraction): 20% (13 votes)
- Moderate hypofractionation (2.5–3.0 Gy/fraction): 70% (46 votes)
- Ultra-hypofractionation/SBRT (>6 Gy/fraction): 10% (7 votes)
- Abstain/unqualified to answer (40 votes)

No consensus.

A combined total of 80% voted in favour of some form of hypofractionated RT in patients with high-risk localised/locally advanced PC undergoing RT to the prostate.

There is no clear evidence for prophylactic irradiation of the pelvic lymph nodes in patients with localised intermediate- or high-risk disease. Long-term results from the NRG/RTOG 9413 trial, which enrolled patients with intermediate- or high-risk PC, showed that neoadjuvant ADT plus whole-pelvis RT improved PFS in comparison to neoadjuvant ADT plus prostate-only RT. However, this survival benefit was accompanied by a higher risk of grade ≥3 gastrointestinal toxicity [25]. The GETUG-01 trial also did not show a significant improvement in event-free survival (EFS) or OS with pelvic nodal irradiation [54]. A single-centre randomised phase 3 trial compared prostate-only RT with whole-pelvis RT in a cohort of 224 patients with clinically node-negative high-risk PC with an estimated risk of >20% of positive nodes (the median estimated node-positive risk according to the Roach formula was 37.8%) [55,56]. The majority of patients had been staged via PSMA PET/CT imaging. After median follow-up of 68 mo, whole-pelvis RT was associated with an improvement in distant MFS and DFS (but not OS), but with a significantly higher rate of late grade ≥2 genitourinary adverse events (17.7% vs 7.5% with prostate-only RT; $p = 0.02$) [55,56].

In the phase 3 randomised POP-RT trial, at median follow-up of 75 mo, the cumulative rate of late urinary CTCAE grade 3 toxicity was low and similar between the whole-pelvis and prostate-only RT groups (5.2% vs 4.1%; $p = 0.49$); rates of grade 2 toxicity were 31.3% versus 22.7% ($p = 0.12$). Long-term patient-reported quality-of-life scores were also similar between the arms [57].

Results from randomised clinical trials such as RTOG 0924 and PIVOTAL-boost are likely to help in better defining the role of whole-pelvis RT in patients with high-risk PC in the coming years.

At APCCC 2024, panellists were asked some questions addressing RT to the pelvic nodes in patients with high-risk localised/locally advanced PC undergoing RT to the prostate.

Q18: In patients with high-risk localised/locally advanced prostate cancer undergoing RT to the prostate, who have had conventional imaging only and are cN0, do you recommend radiation therapy to pelvic nodes?

- Yes, in the majority of patients: 62% (54 votes)
- Yes, but only in selected patients based on risk factors: 25% (22 votes)
- No: 13% (11 votes)
- Abstain/unqualified to answer (19 votes)

No consensus.

A combined total of 87% voted in favour of recommending RT to the pelvic nodes, at least in selected patients.

Q19: In patients with high-risk localised/locally advanced prostate cancer undergoing RT to the prostate, who have had a PSMA PET and are cN0, do you recommend radiation therapy to the pelvic nodes?

- Yes, in the majority of patients: 56% (50 votes)
- Yes, but only in selected patients based on risk factors: 21% (19 votes)
- No: 23% (21 votes)
- Abstain/unqualified to answer (16 votes)

No consensus.

A combined total of 77% voted in favour of recommending RT to the pelvic nodes, at least in selected patients.

3.1.5. Adjuvant treatment considerations in node-negative disease (pN0)

For patients with pN0 disease, risk factors for relapse after surgery include ISUP GG ≥4, pathological stage ≥pT3, and the presence of positive surgical margins (R1) [58].

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Table 1 – Distribution of risk factors in studies evaluating adjuvant versus salvage radiotherapy

Study name	Patients (*n*)		GS ≥8, *n* (%)		pT stage, *n* (%)		R1 status, *n* (%)		pN stage, *n* (%)	
	aRT	sRT	aRT	sRT	aRT	sRT	aRT	sRT	aRT	sRT
GETUG-AFU 17 [61]	212	212	17 (8)	23 (11)	pT3a: 163 (77) pT3b: 45 (21) pT4: 3 (2)	pT3a: 163 (77) pT3b: 43 (20) pT4: 5 (3)	212 (100)	212 (100)	pN0: 163 (73) pNx: 58 (27) pN1: 0	pN0: 151 (71) pNx: 61 (29) pN1: 0
RADICALS-RT [59]	697	699	112 (16)	123 (18)	pT3a: 407 (58) pT3b: 122 (18) pT4: 5 (1%)	pT3a: 389 (56) pT3b: 130 (19) pT3a: 4 (1)	439 (63)	443 (63)	pN0: 335 (48) pNx: 322 (46) pN1: 66 (6)	pN0: 374 (54) pNx: 297 (42) pN1: 28 (4)
RAVES [60]	166	167	25 (15)	27 (15)	pT3a: 135 (81) pT3b: 31 (19%)	pT3a: 134 (80) pT3b: 33 (20)	110 (66)	113 (68)	pN0: NA pNx: NA pN1: 0	pN0: NA pNx: NA pN1: 0

GS = Gleason score; R1 = positive margins; aRT = adjuvant radiotherapy; sRT = salvage radiotherapy; NA = not available.

Three prospective randomised clinical trials (RADICALS-RT, RAVES, and GETUG-AFU 17) compared adjuvant RT to early salvage RT [59–61] (Table 1). Only a minority of patients in these trials had histologically positive nodes (pN1; 5% in RADICALS-RT, <1% in RAVES, and 0% in GETUG-AFU 17). All three trials demonstrated that for patients at risk of biochemical progression, observation followed by early salvage RT at the time of biochemical failure was noninferior to adjuvant RT. In RADICALS-RT, there was no significant difference in bPFS between the two strategies; the urinary incontinence rate was significantly higher in the adjuvant RT group [59]. Similarly, RAVES demonstrated that early salvage RT was noninferior with regard to 5-yr freedom from biochemical progression and was associated with lower rates of genitourinary toxicity [60]. In GETUG-AFU 17, adjuvant RT increased the risk of genitourinary toxicity and erectile dysfunction without increasing EFS in comparison to early salvage RT [61]. Furthermore, the preplanned ARTISTIC meta-analysis of these trials revealed no statistically significant difference in EFS between adjuvant RT and early salvage RT [62]. Long-term results from RADICALS-RT confirmed that adjuvant RT after RP increases the risk of urinary and bowel morbidity and does not meaningfully improve disease control (10-yr freedom from distant metastasis was 93% with adjuvant RT and 90% with early salvage RT; HR 0.68, 95% confidence interval [CI] 0.43–1.07; $p = 0.095$) [63]. Any potential benefit of adjuvant RT is probably limited to a subset of very high-risk patients; this issue warrants further investigation.

The EAU guidelines recommend consideration of adjuvant RT for patients with pT3 N0 PC of ISUP GG 4–5, with or without positive margins [6]. By contrast, the NCCN guidelines recommend that patients with pN0 disease with adverse features (positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA) should undergo monitoring (category 1, preferred) with consideration of early salvage RT in cases with detectable and rising PSA, or alternatively adjuvant RT ± ADT [7].

APCCC 2024 panellists addressed questions on adjuvant treatment after surgery in patients with pN0 disease.

Q23: For the majority of patients with pT3b pN0 following radical prostatectomy with extended PLND and ISUP grade group 4–5 and R0 and with undetectable postoperative PSA, what is your recommendation provided the patient has regained continence?

- Monitoring and early salvage therapy (RT or systemic therapy or both) in case of a confirmed PSA rise: 93% (96 votes)
- Adjuvant therapy (RT or systemic therapy or both): 7% (7 votes)
- Abstain/unqualified to answer (3 votes)

Strong consensus in favour of monitoring and early salvage therapy.

Q24: For the majority of patients with pT3b pN0 following radical prostatectomy with extended PLND and ISUP grade group 4–5 and R1 and with undetectable postoperative PSA, what is your recommendation provided the patient has regained continence?

- Monitoring and early salvage therapy (RT or systemic therapy or both) in case of a confirmed PSA rise: 73% (75 votes)
- Adjuvant therapy (RT or systemic therapy or both): 27% (28 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

The EORTC 22043 randomised trial of adjuvant RT plus 6 mo of ADT failed to accrue. In the RADICALS-RT trial, 24–27% of patients treated with adjuvant RT or salvage RT received neoadjuvant or concomitant/adjuvant ADT for 6 mo; ADT duration was 24 mo in RADICALS-HD and 6 mo in GETUG-AFU-17 [59–61].

APCCC 2024 panellists voted on whether to add adjuvant ADT for patients who are candidates for adjuvant RT.

Q25: If you recommend adjuvant therapy in a patient with pT3b pN0 following radical prostatectomy with extended PLND and ISUP grade group 4–5 and R1 and with undetectable postoperative PSA what is your recommendation regarding systemic therapy?

- Adjuvant radiation therapy alone: 36% (24 votes)
- Adjuvant radiation therapy plus short-term (eg, 6 months) of systemic hormonal therapy: 38% (25 votes)
- Adjuvant radiation therapy plus long-term (eg, 24 months) of systemic hormonal therapy: 24% (16 votes)
- Systemic therapy alone: 2% (1 vote)
- Abstain/unqualified to answer (including I never recommend adjuvant therapy) (40 votes)

No consensus.

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3.1.6. Adjuvant treatment considerations in node-positive disease (pN1)

The presence of histologically positive nodes after surgery (pN1) is a risk factor for relapse [31]. It has been shown that the combination of RP and adjuvant ADT for patients with pN1 disease significantly improves cancer-specific survival and OS [64,65]. However, these studies mostly included patients with high-volume nodal disease and therefore the findings may not apply to patients with less extensive nodal metastases.

Several retrospective studies and a systematic review evaluated the management of patients with pN1 disease after surgery [66–68]. A subset of patients with limited nodal disease (1–2 positive nodes) appear to experience favourable oncological outcomes and thus may not require additional treatment. An analysis of more than 200 patients with one or two positive nodes after surgery showed that 37% remained free of metastases without a need for salvage treatment at median follow-up of 60.2 mo [67]. Therefore, initial observation followed by early salvage RT at the time of relapse may represent a safe option for selected patients with few positive lymph nodes after surgery [68].

APCCC 2024 panellists addressed questions on adjuvant treatment after surgery for patients with pN1 disease.

Q26: For the majority of patients with pT3b and 1–2 pathologically involved pelvic lymph nodes (pN1) following radical prostatectomy with extended PLND and ISUP grade group 4–5 and with undetectable postoperative PSA, what is your recommendation provided the patient has regained continence?

- Monitoring and early salvage therapy (RT or systemic therapy or both) in case of a confirmed PSA rise: 61% (63 votes)
- Adjuvant therapy (RT or systemic therapy or both): 39% (41 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

Q27: If you recommend adjuvant therapy in a patient with pT3b and 1–2 pathologically involved pelvic lymph nodes (pN1) following radical prostatectomy with extended PLND and ISUP grade group 4–5 and with undetectable postoperative PSA, what is your recommendation regarding systemic therapy?

- Adjuvant radiation therapy alone: 3% (2 votes)
- Adjuvant radiation therapy plus short-term (eg, 6 months) of systemic hormonal therapy: 33% (23 votes)
- Adjuvant radiation therapy plus long-term (eg, 24 months) of systemic hormonal therapy: 58% (40 votes)
- Systemic therapy alone: 6% (4 votes)
- Abstain/unqualified to answer (including I never recommend adjuvant therapy) (37 votes)

No consensus.

A combined total of 91% voted in favour of recommending adjuvant RT plus systemic hormonal therapy for cases in which adjuvant therapy is used.

Q28: For the majority of patients with pT3b and 3 or more pathologically involved pelvic lymph nodes (pN1) following radical prostatectomy with extended PLND and ISUP grade group 4–5 and with undetectable postoperative PSA, what is your recommendation provided the patient has regained continence?

- Monitoring and early salvage therapy (RT or systemic therapy or both) in case of a confirmed PSA rise: 39% (41 votes)
- Adjuvant therapy (RT or systemic therapy or both): 61% (63 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

Q29: If you recommend adjuvant therapy in a patient with pT3b and 3 or more pathologically involved pelvic lymph nodes (pN1) following radical prostatectomy with extended PLND and ISUP grade group 4–5 and with undetectable postoperative PSA what is your recommendation regarding systemic therapy?

- Adjuvant radiation therapy alone: 1% (1 vote)
- Adjuvant radiation therapy plus short-term (eg, 6 months) of systemic hormonal therapy: 14% (11 votes)
- Adjuvant radiation therapy plus long-term (eg, 24 months) of systemic hormonal therapy: 78% (60 votes)
- Systemic therapy alone: 7% (5 votes)
- Abstain/unqualified to answer (including I never recommend adjuvant therapy) (29 votes)

Consensus in favour of RT plus long-term ADT for cases in which adjuvant therapy is used.

The Decipher gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment [69]. A meta-analysis showed that Decipher can independently improve patient prognostication after RP [69]. A systematic review has confirmed the clinical utility of this test in post-RP decision-making [70]. It has been shown that in the postoperative setting, Decipher can help in better stratifying at-risk patients who may benefit from immediate adjuvant RT versus observation or salvage RT [71,72]. Further studies are needed to establish how best to incorporate Decipher in clinical practice.

At APCCC 2024, one question addressed the use of genomic classifiers such as Decipher for patients with adverse features after RP.

Q30: For the decision to use adjuvant therapy if adverse features are present post radical prostatectomy do you recommend using a genomic classifier (eg, Decipher) in the majority of patients?

- Yes: 29% (23 votes)
- No: 71% (57 votes)
- Abstain/unqualified to answer (including I do not use a genomic classifier in this situation) (26 votes)

No consensus.

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3.1.7. Discussion on high-risk localised and locally advanced PC

Supplementary Figure 1 provides graphical representations of the voting results for questions on high-risk localised and locally advanced PC.

For cases with discordant MRI and DRE results, there was strong consensus among APCCC 2024 panellists in favour of relying on the MRI findings for tumour staging. However, current international guidelines still recommend basing clinical tumour classification on DRE [6,7]. Because clinical stage heavily influences the therapeutic options offered to patients and directly affects surgery, RT, and systemic therapy recommendations, it seems essential to try to bridge the gap between the guidelines and the consensus opinion of experts and to update the current staging classifications.

At APCCC 2022, 73% of panellists voted to recommend additional imaging (eg, MRI, bone scintigraphy) for the majority of patients with PSMA-positive lesions in bone on PET without a correlate on the CT component. At APCCC 2024, this result was unchanged despite a further 2 yr of clinical experience with PSMA PET/CT. Therefore, it seems that there is still some reluctance to rely solely on PSMA PET uptake in the absence of correlative imaging.

For patients with very high-risk PC, only a minority of the multidisciplinary panellists voted for surgery, preferring RT + long-term ADT ± abiraterone, particularly if patients meet the STAMPEDE criteria for very high-risk localised (M0) PC. These results probably reflect the MFS and OS benefits observed in the STAMPEDE-abiraterone M0 arm, as well as the lack of randomised data showing that RP may be of benefit for patients with very high-risk localised disease [21].

For patients with cN1 disease on conventional imaging, there was strong consensus (92%) in favour of RT plus long-term ADT and 2 yr of abiraterone.

Interestingly, a majority of panellists (74%) voted to allow substitution of another ARPI for abiraterone in patients with high-risk localised/locally advanced M0 disease who are ineligible for abiraterone. Furthermore, although patients in the STAMPEDE trial received 3 yr of ADT and 2 yr of abiraterone, 65% of panellists would stop ADT after 2 yr in the majority of patients.

There is evidence that the sensitivity of PSMA PET/CT for detecting pelvic lymph node involvement is rather low [12,14], and consequently there was no consensus on omitting ePLND or pelvic RT in patients with negative PSMA PET/CT undergoing definitive surgery or RT, respectively.

On the basis of randomised clinical trial results suggesting similar outcomes between adjuvant and salvage RT [59–61], there was strong consensus in favour of monitoring and performing early salvage therapy in the event of PSA rise in patients with pT3b N0 R0 and ISUP GG 4–5. Although there was no consensus, the majority of panellists (73%) also recommended monitoring and early salvage therapy for patients with pT3b N0 and ISUP GG 4–5 and additional R1 disease. This is despite the fact that only a limited number of patients with these high-risk factors were included in the three above mentioned randomised trials comparing adjuvant versus early salvage RT.

For patients with pN1 disease, there was no consensus on adjuvant RT and/or systemic treatment. As suggested by guidelines, the number of positive nodes influenced panellists' treatment choice: for patients with one or two positive nodes, 39% of panellists recommended adjuvant RT and/or systemic therapy while 61% recommended this strategy for patients with three or more positive nodes.

Although some genomic classifiers such as the Decipher score have demonstrated promising results in predicting the risk of recurrence, less than one-third of the panellists recommended use of such a score for the majority of patients with adverse features after surgery. These results may be influenced by the limited accessibility of these molecular tests and the lack of prospective data indicating predictive ability for treatment selection. In fact, the Decipher test is currently not locally available in most regions of the world outside of North America.

3.2. PSA persistence and BCR

3.2.1. PSA persistence

PSA persistence is a post-RP disease state that is most often defined as detectable PSA of $\geq$0.1 ng/ml 4–8 wk after RP [73]. With the greater adoption of ultrasensitive PSA tests, there is variability in defining PSA persistence at a lower threshold such as 0.05 ng/ml, but the important point is that PSA never became undetectable after surgery. Persistent PSA should be a trigger for consideration of early salvage RT. PSA persistence after RP is a negative prognostic factor and is associated with worse outcomes [74–79].

However, in a BCR population receiving salvage RT, there was no clear association between PSA persistence and oncological outcomes [80]. In the randomised phase 3 NRG/RTOG 9601 trial, 44% of patients had a persistently elevated PSA after RP. At median follow-up of 13 yr, there were no significant differences between groups with and without PSA persistence. The 12-yr rates were 56% versus 56% for biochemical failure (p = 0.91), 19% versus 18% for distant metastasis (p = 0.72), and 11% versus 9% for PC-specific mortality (p = 0.32); the OS rate was 26% in both groups (p = 0.95) [80]. On univariable and multivariable analyses, persistently elevated PSA was not significantly associated with any oncological endpoint and did not impact the benefit of long-term hormone therapy. It has been shown that salvage RT improves OS and PC-specific mortality in patients with PSA persistence in comparison to patients who did not receive salvage RT. Thus, in general, patients with PSA persistence should be treated analogously to patients with BCR who have similar characteristics and should be eligible to receive salvage RT and appropriate systemic therapy [80].

Limited randomised trials have included patients with PSA persistence. Trials evaluating the benefit of hormone therapy in patients receiving salvage RT varied in their inclusion of patients with PSA persistence; NRG/RTOG 9601 allowed enrolment of men with PSA persistence, while GETUG-AFU-16 and RADICALS-HD did not [80–82]. NRG GU-002 is one of the few trials that required persistent PSA after RP; patients were randomised to salvage RT and short-term ADT with or without docetaxel. The trial has finished enrolling, but results were not available at the time of writing. The rationale for only including patients with PSA persistence was based on a prior single-arm trial that appeared to demonstrate a greater benefit in this population [83].

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PSMA PET/CT can identify residual cancer after RP, with positivity rates that correlate with the PSA level [84,85]. In cases with persistent PSA, patients may already have metastases to the pelvic nodes or distant sites, which would support the role of PSMA PET/CT imaging in guiding salvage treatment strategies [84].

At APCCC 2024, a number of questions addressed risk factors commonly used in the setting of PSA persistence and BCR.

Q31: What do you recommend for a patient with PSA persistence with a PSA value around 0.2 ng/ml post RP and pN0 on extended PLND and no evidence of risk factors (risk factors: R1, pT3, ISUP grade group 4–5) and a negative postoperative PSMA PET, provided the patient has regained continence?

- Monitoring (including imaging) and salvage therapy in case of further PSA rise: 56% (59 votes)
- Immediate therapy (RT or systemic therapy or both): 44% (46 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

Q32: What do you recommend for a patient with PSA persistence with a PSA value around 0.7 ng/ml post RP and pN0 on extended PLND and no evidence of risk factors (risk factors: R1, pT3, ISUP grade group 4–5) and a negative postoperative PSMA PET, provided the patient has regained continence?

- Monitoring (including imaging) and salvage therapy in case of further PSA rise: 18% (19 votes)
- Immediate therapy (RT or systemic therapy or both): 82% (87 votes)
- Abstain/unqualified to answer (0 votes)

Consensus in favour of immediate therapy in patients with a PSA level of 0.7 ng/ml.

Q33: For patients with PSA persistence post RP and pN0 on extended PLND and no evidence of risk factors (risk factors: R1, pT3, ISUP grade group 4–5) and a negative postoperative PSMA PET that you treat with immediate therapy, what do you recommend?

- Radiation therapy prostate bed alone: 24% (22 votes)
- Radiation therapy prostate bed plus pelvis: 6% (5 votes)
- Radiation therapy prostate bed plus short-term systemic therapy: 16% (15 votes)
- Radiation therapy prostate bed plus pelvis plus short-term systemic therapy: 34% (31 votes)
- Radiation therapy prostate bed plus long-term systemic therapy: 3% (3 votes)
- Radiation therapy prostate bed plus pelvis alone plus long-term systemic therapy: 15% (14 votes)
- Systemic therapy alone: 2% (2 votes)
- Abstain/unqualified to answer (including I do not recommend immediate therapy) (14 votes)

No consensus.

A combined total of 98% voted in favour of RT with or without systemic therapy.

Q34: What do you recommend for a patient with PSA persistence post RP, pN0 on extended PLND and 2 or more risk factors (risk factors: R1, pT3, ISUP grade group 4–5) and a negative postoperative PSMA PET, provided the patient has regained continence?

- Monitoring (including imaging) and salvage therapy in case of further PSA rise: 13% (14 votes)
- Immediate therapy (RT or systemic therapy or both): 87% (91 votes)
- Abstain/unqualified to answer (1 vote)

Consensus in favour of immediate therapy for patients with PSA persistence and risk factors.

Q35: For patients with PSA persistence post RP, pN0 on extended PLND and 2 or more risk factors (risk factors: R1, pT3, ISUP grade group 4–5) and a negative postoperative PSMA PET that you treat with immediate therapy, what do you recommend?

- Radiation therapy prostate bed alone: 6% (6 votes)
- Radiation therapy prostate bed plus pelvis: 4% (4 votes)
- Radiation therapy prostate bed plus short-term systemic therapy: 15% (15 votes)
- Radiation therapy prostate bed plus pelvis plus short-term systemic therapy: 38% (37 votes)
- Radiation therapy prostate bed plus long-term systemic therapy: 8% (8 votes)
- Radiation therapy prostate bed plus pelvis plus long-term systemic therapy: 29% (28 votes)
- Systemic therapy alone: 0% (0 votes)
- Abstain/unqualified to answer (including I do not recommend immediate therapy) (8 votes)

No consensus.

A combined total of 90% voted in favour of recommending RT of the prostate bed ± pelvis plus systemic therapy.

3.2.2. BCR after RP

The risk of BCR after RP varies considerably. For example, at 10 yr after RP in the ProtecT trial, which predominately enrolled patients with low-risk disease, 25% had developed BCR [86], while in the RADICALS-RT trial in predominately intermediate-risk patients, approximately 50% developed recurrence [63] and more than 80% of patients with high-risk disease in the CALGB trial developed BCR [87].

The PSA level that defines BCR varies among guidelines and clinical trials. In general, BCR is defined as a detectable and confirmed rising PSA, with some guidelines not defining a lower PSA limit (EAU guidelines) [73], some defining it as PSA $\geq$0.1 ng/ml (NCCN guidelines) [7], and some defining as PSA $\geq$0.2 ng/ml (American Association of Urology [AUA]/American Society for Radiation Oncology/ASCO guidelines) [88]. Most guidelines recommend a confirmatory PSA test. In addition, some experts advocate for a prognostic risk-adapted approach (ie, a lower PSA threshold for patients with higher prognostic risk).

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BCR is a commonly misunderstood disease state, as one would generally assume that recurrent disease is always associated with higher risk of PC-specific mortality. In reality, this is not the case: although BCR after RP is associated with worse prognosis, many patients have favourable long-term outcomes [89–91]. While BCR is prognostic, it has repeatedly been shown that BCR is not be a suitable surrogate endpoint for OS. This is driven by the fact that many patients who develop BCR after RP can be effectively treated with salvage RT ± ADT; in addition, competing risks of other-cause mortality remain the predominant cause of death, and most patients who experience BCR after RP will not progress to distant metastases within the next 10 yr [89–91].

Unlike localised PC, which is commonly risk-stratified into four to six prognostic groups, BCR has historically been grouped into one large category. However, BCR is actually a heterogeneous and evolving disease state, and the NCCN and EAU guidelines have recently recognised important prognostic factors [6,7]. Examples of factors associated with poor outcomes include absolute PSA after RP, PSA doubling time (PSA-DT), pathological grade and stage, and time to BCR [89]. The EAU guidelines have defined low-risk and high-risk BCR categories on the basis of expert opinion and retrospective data that have yet to be clearly validated as appropriate for guiding salvage RT, ADT, ARPI, or other treatments, but are prognostic for outcomes [89,92]. In addition, a recent AUA guideline defines a BCR category with high-risk features for guiding treatment decisions; these features include PSA $\geq$0.7 ng/ml, Gleason grade group 4–5, PSA-DT $\leq$6 mo, persistently detectable PSA after surgery, and seminal vesicle involvement [93].

Given that salvage RT is the primary salvage modality recommended after RP for patients with BCR, categorisation is often based on PSA at the time of salvage RT. Early salvage RT is often defined as RT at PSA $\leq$0.5 ng/ml, and late salvage RT as RT at PSA >0.5 ng/ml [94,95]. Others have added a very early salvage RT group, defined as patients with any detectable PSA <0.2 ng/ml [96,97]. The long-term success of salvage RT is closely correlated with PSA at the time of salvage RT, and randomised trials such as NRG/RTOG 9601 demonstrated a clear reduction in the development of distant metastases or death from PC when salvage RT ± hormone therapy is used at lower PSA levels [95]. Thus, the NCCN and other guidelines recommend salvage RT at the time of BCR (PSA 0.1–0.2 ng/ml), which is consistent with triggers for salvage RT in trials such as RADICALS-RT [7,63].

PSMA PET/CT is further changing the landscape of what was historically called BCR. For example, among patients with BCR after RP and PSA <0.5 ng/ml, studies estimate that approximately 40% will have PSMA-positive disease on PET/CT that may impact treatment decisions [84,85]. In addition, when considering the EMBARK trial of patients with a unique definition of high-risk BCR without evidence of disease on traditional imaging (CT and bone scan), studies estimate that at least 85% would have PSMA-positive PET/CT findings [98,99]. The best way to incorporate PSMA PET/CT findings remains an area of active investigation, since large phase 3 trials that define our current standards of care did not mandate PSMA PET/CT in the BCR setting.

Q36: For the majority of patients with slowly rising PSA (total PSA value 0.2 ng/ml) after radical prostatectomy and PSA-DT >1 year AND pathological ISUP grade group <4, do you recommend PSMA PET imaging?

- Yes: 58% (61 votes)
- No, PSA monitoring: 27% (28 votes)
- No, early salvage therapy without PSMA PET imaging: 15% (16 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

The use of hormone therapy with salvage RT has been investigated in multiple phase 3 trials. The first was NRG/RTOG 9601, which randomised patients to receive salvage RT ± 2 yr of daily bicalutamide 150 mg [95]. In the overall study population, there was a significant improvement in OS, but there was a significant treatment interaction with the PSA level before salvage RT. Patients in the prespecified PSA <1.5 ng/m category derived no significant OS benefit; this was most clearly observed for patients with PSA <0.7 ng/ml [95]. GETUG-AFU16, which randomised patients to salvage RT ± 6 mo of ADT, met its primary endpoint of improvement in PFS [81]. Unlike RTOG 9601, in which late salvage RT predominated, GETUG-AFU-16 primarily involved early salvage RT. There was no OS improvement in this early salvage RT population [81]. The NRG/RTOG 0534 trial randomised patients to salvage prostate-bed RT, salvage prostate-bed RT + short-term ADT, or salvage prostate-bed + pelvic-lymph-node RT + short-term ADT [100]. RTOG 0534 arms 1 and 2 mirrored the GETUG-AFU-16 trial, with early salvage RT predominating, and similarly found a BCR/PFS benefit but no OS benefit with addition of short-term ADT to salvage RT [100]. Most recently, RADICALS-HD involved multiple randomised groups in the salvage RT setting: 0 mo versus 6 mo of ADT; 6 mo versus 24 mo of ADT; and 0 mo versus 6 mo versus 24 mo of ADT [82,101]. RADICALS-HD was unique in that it also included patients receiving adjuvant RT, but like GETUG-AFU-16 and RTOG 0534, the majority of patients received early salvage RT. RADICALS-HD demonstrated that 6 mo of ADT did not improve MFS or OS outcomes in comparison to salvage RT alone [82,101]. There also was no difference in MFS or OS between the three-way randomised trial of 0 mo versus 6 mo versus 24 mo of ADT, although this study was underpowered. In terms of MFS, 24 mo of ADT was superior to 6 mo of ADT when added to salvage RT. Patients in this randomisation had higher PSA before salvage RT and more adverse prognostic features [82]. The DADSPORT meta-analysis presented at the 2022 European Society for Medical Oncology (ESMO) congress assessed data from NRG/RTOG 9601, GETUG-AFU 16, NRG/RTOG 0534, and RADICALS-HD and revealed no clear evidence of an improvement in OS [102]. In general, while taking into account differences among patient populations and the types and durations of hormone therapy in each trial, hormone therapy seems to add more benefit in patients with higher PSA before salvage RT and/or multiple adverse prognostic features, including adverse Decipher or ArteraAI scores.

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The panel voted on two questions related to BCR in patients with EAU low-risk criteria (definition in the Supplementary material).

Q37: For the majority of patients with slowly rising PSA (total PSA value 0.2 ng/ml) after radical prostatectomy and PSA-DT >1 year AND pathological ISUP grade group <4, if you recommended PSMA PET imaging and PSMA PET is negative, what do you recommend?

- Early salvage therapy (RT ± systemic therapy): 61% (55 votes)
- Regular imaging, eg, every 4–12 months: 15% (13 votes)
- Repeat PSMA PET every time PSA doubles: 24% (22 votes)
- Abstain/unqualified to answer (including I did not recommend PSMA PET) (16 votes)

No consensus.

Q38: For the majority of patients with a confirmed rising PSA after radical prostatectomy and PSA-DT >1 year AND pathological ISUP grade group <4 and no or negative PSMA PET imaging, what is your management recommendation regarding salvage therapy?

- Radiation therapy alone: 49% (47 votes)
- Radiation therapy plus short-term (eg, 6 months) of systemic hormonal therapy: 43% (41 votes)
- Radiation therapy plus long-term (eg, 24 months) of systemic hormonal therapy: 6% (6 votes)
- Systemic therapy alone: 2% (2 votes)
- Abstain/unqualified to answer (including I did not vote for salvage therapy) (10 votes)

No consensus.

A combined total of 98% voted in favour of RT with or without systemic therapy.

The panel voted on six questions related to BCR in patients with EAU high-risk criteria (definition in the Supplementary material).

Q39: For the majority of patients with a confirmed rising PSA after radical prostatectomy (WITHOUT risk factors for local relapse ≥pT3b and/or R1) and PSA-DT <1 year OR pathological ISUP grade group 4–5 (EAU high-risk), what management do you recommend?

- Salvage RT (± systemic therapy) as early as possible (ie, before PSA <0.2 ng/ml): 41% (43 votes)
- Wait until PSA is approximately 0.2 ng/ml and perform PSMA PET: 57% (59 votes)
- Systemic therapy alone: 2% (2 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

Q40: For the majority of patients with a confirmed rising PSA after radical prostatectomy (WITH risk factors for local relapse ≥pT3b and/or R1) and PSA-DT <1 year OR pathological ISUP grade group 4–5 (EAU high-risk), what management do you recommend?

- Salvage RT (± systemic therapy) as early as possible (ie, before PSA <0.2 ng/ml): 63% (66 votes)
- Wait until PSA is approximately 0.2 ng/ml and perform PSMA PET: 37% (38 votes)
- Systemic therapy alone: 0% (0 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

Q41 If you recommend salvage RT in a patient with a confirmed rising PSA but a PSA <0.2 µg/l after radical prostatectomy and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 WITH risk factors for local relapse (≥pT3b and/or R1), at what PSA value do you recommend initiating salvage therapy?

- PSA <0.1 ng/ml: 9% (7 votes)
- PSA 0.1–0.15 ng/ml: 41% (34 votes)
- PSA >0.15 – <0.2 ng/ml: 50% (41 votes)
- Abstain/unqualified to answer (including I do not recommend salvage therapy in patients with a PSA <0.2 ng/ml) (24 votes)

No consensus

Q42: If you recommend salvage RT in a patient with a confirmed rising PSA but a PSA <0.2 µg/l after radical prostatectomy and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 WITHOUT risk factors for local relapse (≥pT3b and/or R1) at what PSA value do you recommend initiating salvage therapy?

- PSA <0.1 ng/ml: 4% (3 votes)
- PSA 0.1–0.15 ng/ml: 34% (25 votes)
- PSA >0.15–<0.2 ng/ml: 62% (45 votes)
- Abstain/unqualified to answer (including I do not recommend salvage therapy in patients with a PSA <0.2 ng/ml) (33 votes)

No consensus.

Q43: For the majority of patients with a confirmed rising PSA after radical prostatectomy and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and no or negative PSMA PET imaging, what is your management recommendation?

- Monitoring: 10% (11 votes)
- Salvage therapy (RT or systemic therapy or both): 90% (94 votes)
- Abstain/unqualified to answer (1 vote)

Strong consensus in favour of salvage therapy.

Q44: For the majority of patients with a confirmed rising PSA after radical prostatectomy and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and no or negative PSMA PET imaging, what is your management recommendation regarding salvage therapy?

- Radiation therapy alone: 11% (11 votes)
- Radiation therapy plus short-term (eg, 6 months) of systemic hormonal therapy: 62% (63 votes)
- Radiation therapy plus long-term (eg, 24 months) of systemic hormonal therapy: 26% (27 votes)
- Systemic therapy alone:1% (1 vote)

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- Abstain/unqualified to answer (including I do not recommend salvage therapy) (4 votes)

No consensus.

A combined total of 88% voted in favour of RT plus systemic hormonal therapy (either short-term or long-term).

Section 3.1.6 described use of the Decipher test to guide the choice of adjuvant therapy after RP. APCCC 2024 panellists voted on use of a test such as Decipher to decide on whether or not to add systemic therapy to salvage RT.

Q45: For the majority of patients with an early rise of PSA after RP, do you recommend using a molecular classifier (eg, Decipher) for the decision to add systemic hormonal therapy to salvage radiation therapy?

- Yes: 28% (24 votes)
- No: 72% (63 votes)
- Abstain/unqualified to answer (including I do not use a molecular classifier routinely in this situation) (19 votes)

No consensus.

3.2.3. RT field size in patients with BCR

NRG/RTOG 0534 is the only phase 3 trial that has reported mature data on the benefit of adding pelvic nodal RT to salvage prostate-bed RT and short-term ADT (arm 2 vs arm 3) [100]. Addition of pelvic-node RT was associated with an improvement in bPFS, but differences in MFS and OS between the arms did not reach the prespecified statistical significance level. Patients with higher PSA before salvage RT appeared to potentially derive greater benefit from nodal RT, which is similar to data on the use of ADT in the salvage RT setting. A secondary analysis of data from RTOG 0534 found that nodal RT appeared to provide a greater benefit in patients who had no PLND at the time of RP, or had fewer than two lymph nodes removed (vs ≥2 lymph nodes) during PLND [103]. It has been shown that nodal RT can potentially increase the risk of side effects [100,104]. Use of PSMA PET/CT to guide treatment is currently being assessed in a randomised study enrolling patients with low-risk BCR after RP [105].

Q46: For the majority of patients with an early rise of PSA after RP and extended PLND (pN0) and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and a negative PSMA PET in which you recommend salvage radiation therapy, what is your preferred approach regarding the RT field?

- Prostate bed radiation therapy alone: 48% (42 votes)
- Prostate bed plus pelvic lymph nodes: 52% (46 votes)
- Abstain/unqualified to answer (18 votes)

No consensus.

Q47: For the majority of patients with an early confirmed rise of PSA after RP without PLND and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and a negative PSMA PET in which you recommend salvage radiation therapy, what is your preferred approach regarding the RT field?

- Prostate bed radiation therapy alone: 14% (13 votes)
- Prostate bed plus pelvic lymph nodes: 86% (77 votes)
- Abstain/unqualified to answer (16 votes)

There was consensus in favour of RT to the prostate bed and pelvic lymph nodes in patients with EAU high-risk biochemical relapse after RP without PLND.

The STORM-PEACE-5 trial randomised patients with oligorecurrent PC with to five PSMA-positive pelvic nodal lesions on PET to receive focal SBRT or elective pelvic nodal irradiation with a boost to the positive nodes; in both arms, patients also received 6 mo of ADT [106]. Irradiation of the prostate bed was not mandatory, but was recommended for patients with pT3 R1 disease. Initial results reported at ESTRO 2024 showed that inclusion of the prophylactic pelvic regions was associated with significantly better biochemical and locoregional relapse-free survival, while omitting the prostate bed was associated with a threefold higher risk of subsequent local recurrence [107].

Q48: In the majority of patients with a confirmed PSA rise after radical prostatectomy without prior salvage RT and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your treatment recommendation regarding the radiation therapy?

- SBRT of positive nodes alone: 3% (3 votes)
- Whole pelvis RT plus/minus boost to positive nodes: 20% (18 votes)
- Radiation therapy prostate bed plus whole pelvis plus/minus boost to positive nodes: 77% (70 votes)
- Abstain/unqualified to answer (15 votes)

There was consensus in favour of RT to the prostate bed plus the whole pelvis with or without a boost to positive nodes.

Q49: In the majority of patients with a confirmed PSA rise after radical prostatectomy with prior salvage RT to the prostate bed and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your treatment recommendation regarding the radiation therapy?

- SBRT of positive nodes alone: 37% (34 votes)
- Whole pelvis RT plus/minus boost to positive nodes: 63% (58 votes)
- Abstain/unqualified to answer (14 votes)

No consensus.

Given the potential morbidity of local salvage options, we asked the panellists if histological confirmation is needed when local relapse is suspected from MRI or PSMA PET/CT findings.

Q50: In the majority of patients with a confirmed PSA rise after radical prostatectomy with PSA-DT >1 year AND pathological ISUP grade group <4 and a local relapse in the prostate bed detected on MRI and/or PSMA PET and N0 M0 (no prior local salvage RT), do you recommend a biopsy?

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- Yes: 18% (19 votes)
- No: 82% (85 votes)
- Abstain/unqualified to answer (2 votes)

There was consensus in favour of not recommending a biopsy.

Q51: In the majority of patients with PSA rise after radical prostatectomy with PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and a local relapse in the prostate bed detected on MRI and/or PSMA PET and N0 M0 (no prior local salvage RT), do you recommend a biopsy?

- Yes: 14% (14 votes)
- No: 86% (89 votes)
- Abstain/unqualified to answer (3 votes)

There was consensus in favour of not recommending a biopsy.

Q52: In the majority of patients with a confirmed PSA rise after radical prostatectomy and a local relapse in the prostate bed detected on MRI and/or PSMA PET and N0 M0 (no prior local salvage RT) confirmed by biopsy and a PSA-DT >1 year AND pathological ISUP grade group 1–3, what do you recommend?

- Monitoring: 2% (2 votes)
- Radiation therapy of the prostatic bed ± boost to the lesion: 41% (41 votes)
- Radiation therapy of the prostatic bed ± boost the lesion plus short-term (eg, 6 months) of systemic therapy: 47% (48 votes)
- Radiation therapy of the prostatic bed ± boost the lesion plus long-term (eg, 24 months) of systemic therapy: 10% (10 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

A combined total of 98% voted in favour of RT ± boost ± systemic therapy.

Q53: In the majority of patients with PSA rise after radical prostatectomy and a local relapse in the prostate bed detected on MRI and/or PSMA PET (no prior local salvage RT) confirmed by biopsy and a PSA-DT ≤1 year or pathological ISUP grade group 4 or 5, what do you recommend?

- Monitoring: 0% (0 votes)
- Radiation therapy of the prostatic bed ± boost to the lesion ± pelvis: 8% (8 votes)
- Radiation therapy of the prostatic bed ± boost the lesion ± pelvis plus short-term (eg, 6 months) of systemic therapy: 56% (57 votes)
- Radiation therapy of the prostatic bed ± boost the lesion ± pelvis plus long-term (eg, 24 months) of systemic therapy: 36% (36 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

A combined total of 100% voted in favour of RT ± boost ± systemic therapy.

The benefit of adding ARPI to salvage RT + ADT was evaluated in a limited number of completed and several ongoing studies. FORMULA 509 randomised patients to receive salvage RT plus 6 mo of ADT ± 6 mo of concurrent abiraterone and apalutamide. The primary endpoint was PFS, which was not improved in the overall trial population [108]. However, in the prespecified subgroup with PSA >0.5 ng/ml, there was a significant improvement in MFS with addition of ARPI therapy. Several ongoing or maturing trials are testing the use of ARPIs in the post-RP BCR setting, including NRG GU006 (apalutamide), STEEL (enzalutamide), DASL-HiCAP (darolutamide), NRG GU008 (apalutamide in pN+ disease), and NRG GU002 (docetaxel) [109].

3.2.4. *BCR after radical prostate RT*

BCR after radical RT is nearly universally defined according to the Phoenix criterion of nadir +2 ng/ml [110]. However, with the increasing use of PSMA PET/CT, some experts advocate for revision of this definition to a lower threshold. In comparison to the setting of BCR after RP, there is a considerably lower quantity and quality of evidence regarding management of patients with BCR after RT. A small number of single-centre and multicentre single-arm trials have been performed, primarily evaluating salvage brachytherapy and SBRT. A systematic review and meta-analysis of studies compared the efficacy and toxicity of salvage RP, salvage high-intensity focused ultrasound (HIFU), salvage cryotherapy, and reirradiation via brachytherapy or SBRT for the management of locally recurrent PC after RT [111]. There were no significant differences in recurrence-free survival between these modalities. However, the authors reported that the rate of severe genitourinary toxicity exceeded 21% for HIFU and surgery, whereas it ranged from 4.2% to 8.1% for reirradiation [111]. Owing to the methodological limitations of this review (the majority of the studies included were uncontrolled single-arm case series, and there was considerable heterogeneity in the definitions of outcomes), the evidence available for these treatment options is of low quality, and no strong recommendations regarding the choice of any of these techniques can be made.

Q54: In patients with high-risk localised/locally advanced prostate cancer who have received radical RT plus systemic therapy (ADT ± ARPI), at what point do you recommend imaging in case of a rising PSA from a nadir of <0.2 ng/ml **in the context of recovering testosterone?**

- At PSA ≥2 ng/ml above nadir: 36% (38 votes)
- At PSA 1–2 ng/ml above nadir and with rapidly rising PSA: 33% (34 votes)
- At PSA 1–2 ng/ml irrespective of PSA kinetics: 31% (32 votes)
- Abstain/unqualified to answer (including I do not recommend imaging at imaging at all in this setting) (2 votes)

No consensus.

Q55: What do you recommend for the majority of patients with a confirmed local recurrence in the prostate after radical RT (interval to biochemical failure <18 months and/or ISUP grade group 4–5) and a PSA-DT ≤9 months and no detectable metastases on imaging?

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- Local salvage therapy (± systemic therapy): 68% (71 votes)
- Systemic therapy alone: 28% (30 votes)
- Monitoring: 4% (4 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

A combined total of 96% voted in favour of an active treatment modality.

Q56: If you use local salvage therapy in a patient with a confirmed local recurrence in the prostate after radical RT (interval to biochemical failure <18 months and/or ISUP grade group 4–5) and a PSA-DT ≤9 months and no detectable metastases on imaging, what do you recommend?

- Salvage prostatectomy: 37% (28 votes)
- SBRT re-irradiation: 30% (23 votes)
- Brachytherapy alone: 15% (11 votes)
- Other local therapy, such as HIFU or cryotherapy or irreversible electroporation (IRE): 18% (14 votes)
- Abstain/unqualified to answer (including I do not recommend a local salvage therapy) (30 votes)

No consensus.

3.2.5. *High-risk BCR (nonmetastatic HSPC on conventional imaging)*

Results from the randomised phase 3 EMBARK trial were published in 2023 [99]. This trial enrolled patients with nonmetastatic high-risk BCR, defined as PSA-DT ≤9 mo and PSA ≥2 ng/ml above the nadir after RT, or ≥1 ng/ml above the nadir after RP with or without postoperative RT. This definition differs from the EAU definition of high-risk BCR (PSA-DT ≤1 yr or pathological ISUP GG 4–5 in patients treated with RP; time to biochemical failure ≤18 mo or biopsy ISUP GG 4–5 in patients treated with RT) [89].

Conventional imaging was used for staging in EMBARK. Among the patients, 25% had previously undergone RP alone, 26% received RT alone, and 49% underwent both RP and postoperative RT. Median PSA was 5.0 ng/ml, median PSA-DT was 4.6 mo, and one-third of the patients had GS ≥8. Patients were randomised to receive 9 mo of ADT alone, enzalutamide alone, or enzalutamide + ADT. In terms of MFS, combination therapy and enzalutamide alone were both superior to ADT alone; MFS was also numerically greater with ADT plus enzalutamide than with enzalutamide alone, but this comparison was not part of the statistical analysis plan [99]. It should be noted that MFS in this setting of BCR may differ from MFS as a surrogate intermediate clinical endpoint for locally advanced PC validated by the ICECaP consortium [112]. In addition, approximately 40% of MFS events in EMBARK were deaths from other causes, and up to 60% of participants died from causes other than PC. The rate of ischaemic cardiac events was numerically higher in the enzalutamide monotherapy arm than in the ADT monotherapy arm and in the combination arm (enzalutamide + ADT). Gynaecomastia and nipple sensitivity were also uniquely more frequent in the enzalutamide monotherapy arm. EMBARK required suspension of treatment at week 37 if PSA decreased to <0.2 ng/ml, and treatment was restarted when PSA reached >5.0 ng/ml in patients without previous RT, or at least 2.0 ng/ml in patients with previous RP [99].

APCCC 2024 panellists voted on what treatment to recommend in an EMBARK-like scenario if conventional imaging (as in EMBARK) or PSMA PET/CT were used.

Q57: For the majority of patients with a confirmed rising PSA (≥1 ng/ml after RP) and no prior salvage RT and PSA-DT ≤9 months and normal testosterone and negative conventional imaging, what do you recommend?

- PSMA PET imaging: 79% (83 votes)
- Salvage RT ± systemic therapy: 19% (20 votes)
- Immediate systemic therapy: 2% (2 votes)
- Monitoring only, and deferred treatment: 0% (0 votes)
- Abstain/unqualified to answer (1 vote)

There was consensus in favour of recommending PSMA PET/CT imaging.

Q58: For the majority of patients with high-risk nmHSPC and oligometastatic disease on PSMA PET imaging, what do you recommend?

- Immediate systemic therapy: 15% (15 votes)
- Immediate metastasis directed therapy: 14% (15 votes)
- Immediate combination of both options above: 70% (73 votes)
- Monitoring only and deferred treatment: 1% (1 vote)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 99% voted in favour of immediate treatment.

Q59: For the majority of patients with high-risk nmHSPC and oligometastatic disease on PSMA PET imaging, what do you recommend for systemic therapy?

- ADT alone, intermittent therapy: 7% (7 votes)
- ADT alone, continuous therapy: 4% (4 votes)
- ADT plus ARPI, intermittent therapy: 52% (52 votes)
- ADT plus ARPI, continuous therapy: 30% (30 votes)
- ARPI alone, intermittent therapy: 6% (6 votes)
- ARPI alone, continuous therapy: 1% (1 vote)
- Abstain/unqualified to answer (Including I do not recommend systemic therapy in this situation) (6 votes)

No consensus.

A combined total of 82% voted in favour of ADT plus ARPI (continuous or intermittent).

Q60: For the majority of patients with high-risk nmHSPC and negative PSMA PET imaging, what do you recommend?

- Immediate systemic therapy: 70% (73 votes)
- Monitoring and deferred treatment: 30% (31 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

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Q61: For the majority of patients with high-risk nmHSPC and negative PSMA PET imaging, what do you recommend for systemic therapy?

- ADT alone, intermittent therapy: 15% (14 votes)
- ADT alone, continuous therapy: 3% (3 votes)
- ADT plus Enza, intermittent therapy: 51% (47 votes)
- ADT plus Enza, continuous therapy: 21% (20 votes)
- Enza alone, intermittent therapy: 8% (7 votes)
- Enza alone, continuous therapy: 2% (2 votes)
- Abstain/unqualified to answer (including I do not recommend systemic therapy in this situation) (13 votes)

No consensus.

A combined total of 90% voted in favour of ADT-based treatment rather than enzalutamide monotherapy.

Q62: Is it appropriate to extrapolate the data generated by the EMBARK trial with enzalutamide to other ARPI (apalutamide and darolutamide for monotherapy, apalutamide, darolutamide and abiraterone for combination therapy)?

- Yes: 57% (58 votes)
- No: 43% (43 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

Results from the EMBARK trial may increase interest in AR antagonist monotherapy. Therefore, it will be important to know how to manage patients who progress on AR antagonist monotherapy.

Q63: For the majority of patients progressing on an AR antagonist (Apa, Daro, Enza) monotherapy without ADT, what is your treatment recommendation in case of unequivocal radiographic progression (not eligible for metastases directed therapy)?

- Continue the AR antagonist monotherapy and start ADT: 62% (61 votes)
- Discontinue the AR antagonist and start ADT monotherapy: 12% (12 votes)
- Discontinue the AR antagonist and start ADT plus an additional systemic treatment: 26% (26 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

3.2.6. Discussion on PSA persistence and BCR

Supplementary Figure 2 provides graphical representations of the voting results for questions on PSA persistence and BCR.

In recent years, the historical focus on demonstrating a benefit of adjuvant RT has almost completely transitioned to investigating how to optimally risk-stratify and manage patients with PSA persistence or BCR, which has given rise to several treatment controversies in this setting. Numerous large randomised trials in the PSA persistence and/or BCR setting are under way; their results will help in better defining which patients should receive salvage RT to the prostate bed and/or nodal regions, the optimal use and duration of ADT, chemotherapy, and ARPI therapy, and the role of biomarkers such as luminal/basal subtyping, PORTOS (a 24-gene postoperative RT outcomes score), Decipher, and ArteraAI (a multimodal artificial intelligence–based test that combines digital images on biopsy with clinical data for individual patients to predict PC therapy benefit and prognosticate long-term outcomes).

For patients with PSA persistence, there was no consensus on what type of treatment to recommend. However, there was consensus that immediate treatment is warranted if patients have higher persistent PSA after RP.

On the basis of established prognostic factors for patients with BCR after RP or RT, the EAU guidelines proposed low-risk and high-risk categories (for patients after RP or RT). For patients with BCR meeting the low-risk criteria, the EAU guidelines include a weak recommendation for monitoring instead of salvage therapy [73,89,92]. For patients with low-risk BCR (EAU definition) after RP, there was no APCCC consensus regarding the role of PSMA PET/CT, and approximately a quarter of the panellists voted for PSA monitoring in this specific situation, reflecting the often indolent course of the disease in these patients.

There was no consensus on precise triggers for salvage RT, but it was generally recommended that RT should be given as either very early salvage RT (PSA <0.2 ng/ml) or early salvage RT (PSA 0.2–0.5 ng/ml). There was strong consensus in favour of recommending salvage therapy (salvage RT, systemic therapy, or both), for patients with EAU high-risk BCR; 88% of panellists would recommend salvage RT plus 6 mo or 24 mo of systemic therapy. There was no consensus on when to use ADT with salvage RT or what ADT duration is optimal with this combination.

There also was no consensus on whether to use a Decipher test to decide on whether to add systemic treatment to salvage RT. This test is largely unavailable outside the USA, which may have driven the lack of consensus, even though the questions direct panellists to assume that all tests are available. Thus, for many clinicians, the choice of salvage treatment continues to rely exclusively on clinical factors, even though data supporting the Decipher test are far superior to those supporting, for example, the EAU definition of risk [71–73].

Regarding the RT field for patients with EAU high-risk BCR, there was consensus in favour of recommending RT to the prostate bed and pelvic lymph nodes for patients with negative PSMA PET/CT findings and for patients with positive nodes on PSMA PET/CT. There was also consensus in favour of not recommending biopsy for patients with suspected local relapse in the prostate bed detected on MRI and/or PSMA PET/CT, independent of EAU BCR risk category.

For the management of BCR after radical RT, there was no consensus on either when to perform imaging or the optimal salvage treatment. This lack of consensus is probably driven by multiple factors, including limited availability of local salvage therapies, as not all practices have historically offered salvage RP, salvage brachytherapy, or other ablative therapies. It is only more recently that results have demonstrated that salvage SBRT, which is more widely available, is safe and effective. Thus, trials are warranted to better understand the optimal management of locally recurrent disease after radical RT.

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Despite the recent publication of results from EMBARK, no consensus was reached on the optimal treatment for patients with high-risk PSA relapse according to the EMBARK definition. The majority of panellists would recommend an ADT-based regimen and not an AR antagonist alone for the majority of patients. Only a few panellists chose the option "abstain", which included not offering systemic treatment in this situation. Given the higher risk of side effects with systemic therapy, personalisation of use is warranted when treating patients with asymptomatic BCR, especially considering that PSMA PET/CT findings are likely to be positive for most of these patients.

3.3. mHSPC

3.3.1. Terminology

For APCCC 2024, high metastatic burden was defined as a high volume (CHAARTED) of high-risk (LATITUDE) metastatic disease, and low metastatic burden otherwise.

Different terminologies are used for various PC clinical states and associated treatments, which can be confusing for clinicians and can cause distress for patients [113,114]. APCCC 2024 panellists tried to reach a consensus regarding terminology.

Q64: What terminology do you recommend using for the drugs abiraterone, apalutamide, enzalutamide and darolutamide?

- Androgen receptor pathway inhibitors (ARPI): 58% (62 votes)
- Androgen receptor signalling inhibitors (ARSI): 20% (21 votes)
- Androgen receptor-targeted agents (ARTA): 8% (9 votes)
- Second generation ARPIs (SARPI): 4% (4 votes)
- New hormonal agents (NHA): 5% (5 votes)
- Novel hormonal therapies (NHT): 5% (5 votes)
- Abstain/unqualified to answer (0 votes)

No consensus.

The term "ARPI" is used throughout this paper.

Q65: Which terminology do you recommend for newly diagnosed metastatic disease?

- Metastatic hormone sensitive prostate cancer (mHSPC): 65% (69 votes)
- Metastatic hormone naïve prostate cancer (mHNPC): 19% (20 votes)
- Metastatic castration sensitive prostate cancer (mCSPC): 16% (17 votes)
- Abstain (including I recommend another term) (0 votes)

No consensus.

The term "mHSPC" is used throughout this paper.

Q66: Which terminology do you recommend using in patients with mHSPC that receive ADT plus an additional systemic therapy?

- Combination systemic therapy: 17% (18 votes)
- Systemic treatment intensification: 25% (26 votes)
- Doublet or triplet therapy: 58% (62 votes)
- Abstain (including I recommend another term) (0 votes)

No consensus.

3.3.2. Triplet systemic therapy

Two phase 3 clinical trials, PEACE 1 and ARASENS, showed that triplet systemic therapy consisting of ADT plus six cycles of docetaxel plus abiraterone or darolutamide improves OS in comparison to doublet therapy consisting of ADT plus six cycles of docetaxel [115,116]. To date, there is no randomised evidence on whether systemic triplet therapy improves outcomes in comparison to doublet therapy with ADT plus an ARPI [117]. In PEACE-1, a benefit of systemic triplet therapy in terms of radiographic PFS (rPFS) was observed for patients with either low-burden or high-burden disease. An OS benefit was also observed for patients with high-burden disease, but OS data for patients with low-burden disease are not yet mature. Of note, all patients in PEACE-1 had synchronous metastatic disease and therefore were at higher risk overall [115]. For patients with mHSPC receiving ADT alone, in addition to volume of disease, time of metastatic presentation (synchronous vs metachronous) appeared to be a prognostic factor [118]. Post hoc subgroup analyses of ARASENS suggested that the benefit of the triplet regimen was similar regardless of disease volume or timing of metastatic presentation [116,119]. However, this also was a relatively higher-risk population: 87% had synchronous M1 disease and 70% had disease defined as "high volume" [119]. The phase 3 ENZAMET trial included participants with a wider range of prognostic factors: 45% received concurrent docetaxel (at the investigator's discretion); planned use of docetaxel was a stratification factor, but treatment with docetaxel was not randomised [120]. Triplet systemic therapy in ENZAMET resulted in an OS HR of 0.73 for patients with synchronous metastases. No OS benefit was observed with triplet systemic therapy in ENZAMET for patients with metachronous disease, although the sample size was small [120].

Of note, a meta-analysis of individual patient data from studies evaluating addition of docetaxel alone to ADT found no evidence that docetaxel provided relevant improvements in oncological outcomes for patients with low-volume metachronous disease [121,122].

APCCC 2024 panellists voted on questions regarding the use of systemic triplet therapy in different scenarios.

Q67: In patients with high-burden mHSPC that are chemotherapy fit, do you recommend the triplet therapy ADT plus docetaxel plus ARPI?

- Yes, in the majority of patients: 54% (56 votes)
- Yes, but only in selected patients: 40% (42 votes)
- No, I usually do not recommend this combination: 6% (6 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 94% voted in favour of recommending triplet therapy either for the majority or at least for selected patients.

Q68: If you use the triplet therapy (ADT plus docetaxel plus ARPI) only in selected patients, what is most important factor for your decision to use triplet therapy?

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- Synchronous disease (versus metachronous): 31% (28 votes)
- Age (biological): 12% (11 votes)
- High volume disease (versus low volume): 57% (51 votes)
- Abstain/unqualified to answer (I did not vote for triplet therapy in selected patients) (16 votes)

No consensus.

Q69: In patients with synchronous low-burden mHSPC that are chemotherapy fit, do you recommend the triplet therapy ADT plus docetaxel plus ARPI?

- Yes, in the majority of patients: 3% (3 votes)
- Yes, but only in selected patients: 47% (49 votes)
- No: 50% (53 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

Q70: In patients with metachronous low-burden mHSPC that are chemotherapy fit, do you recommend the triplet therapy ADT plus docetaxel plus ARPI?

- Yes, in the majority of patients: 2% (2 votes)
- Yes, but only in selected patients: 14% (15 votes)
- No: 84% (88 votes)
- Abstain/unqualified to answer (1 vote)

There was consensus against recommending triplet therapy for patients with metachronous low-burden mHSPC.

Q71: In patients with metachronous high-burden mHSPC that are chemotherapy fit, do you recommend the triplet therapy ADT plus docetaxel plus ARPI?

- Yes, in the majority of patients: 34% (35 votes)
- Yes, but only in selected patients: 50% (51 votes)
- No: 16% (16 votes)
- Abstain/unqualified to answer (4 votes)

No consensus.

A combined total of 84% voted in favour of recommending triplet therapy in at least selected patients with metachronous high-burden mHSPC.

In December 2017, two docetaxel-related deaths occurred in the PEACE-1 trial [115]. Both deaths were due to neutropenic fever; granulocyte colony stimulating factor (G-CSF) had been recommended but was not mandated by the study protocol. Health authorities permitted the trial to be restarted on the condition that an amendment be made to mandate prescription of G-CSF. After this amendment was authorised, no additional toxicity-related deaths were observed [115].

Q72: For patients with mHSPC that receive triplet therapy (ADT plus docetaxel plus ARPI), do you routinely recommend primary G-CSF prophylaxis?

- Yes, in the majority of patients: 25% (22 votes)
- Yes, but only in selected patients: 18% (16 votes)
- No: 57% (50 votes)
- Abstain/unqualified to answer (18 votes)

No consensus.

3.3.3. *Synchronous mHSPC*

Several randomised clinical trials showed that addition of an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT improved OS in comparison to ADT alone, regardless of disease volume (low or high) and/or time of metastasis presentation (synchronous or metachronous) [123–127]. In general, more data are available for patients with synchronous mHSPC, as patients with metachronous disease were either excluded or were a minority of participants in most studies.

RT to the primary tumour did not improve OS in the overall population in any of the three randomised trials that tested this hypothesis in mHSPC [115,128,129]. For patients with low-burden synchronous mHSPC, RT to the primary tumour in addition to ADT improved OS in a subgroup analysis (prespecified and prepowered) for one study (STAMPEDE) but not in the two other phase 3 trials (HORRAD and PEACE-1) [115,128–130]. In all three studies, conventional imaging was used for staging. The only evidence regarding the effect of adding both RT to the primary tumour and an ARPI to the standard of care (SOC) for patients with PC comes from PEACE-1 [115,130]. For patients with low-volume disease, SOC (ADT ± docetaxel) plus abiraterone plus RT to the primary tumour improved rPFS, but not OS, in comparison to SOC plus abiraterone [130]. In the PEACE-1 trial, RT to the primary tumour seemed to improve the time to serious genitourinary events in patients with low-burden disease and in the overall study population. Details of serious genitourinary events were reported only for the low-burden population and included receipt of a urinary catheter or double-J stent, nephrostomy, prostate RT, TURP, and RP; a major difference was seen for prostate RT and TURP. However, these data have only been reported and have not yet been published [130].

Since all the studies that evaluated combination systemic therapies and RT to the primary tumour used conventional imaging, it is unclear if we can extrapolate the results to patients with metastatic disease diagnosed via next-generation imaging such as PSMA PET/CT. Therefore, in daily practice, clinicians face the increasingly challenging question of which treatment(s) to recommend for patients with synchronous oligometastatic PC. There is no randomised trial evidence for synchronous oligometastatic HSPC suggesting a benefit of systemic therapy plus treatment of the primary tumour plus metastasis-directed therapy (MDT) for all metastases, nor is there a formal and generally accepted definition of this oligometastatic stage.

Four ingle-arm studies have reported outcomes for a total of 123 patients with oligometastatic HSPC who received multimodal treatment including ADT ± ARPI ± docetaxel, treatment of the primary tumour (if patients had synchronous disease), and MDT. Undetectable PSA levels were achieved in 20–80% of patients [131–134]. In one study of 39 patients with up to two bone metastases on conventional imaging, the 4-yr BCR-free survival rate was 53% [134]. All these trials had small sample sizes and were not phase 3 studies, and thus their results should be interpreted with caution.

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In addition, the optimal duration of systemic therapy in these situations remains unclear. In particular, for patients with low-burden disease who receive local therapy to the primary tumour and all metastases, the question of whether they should also receive lifelong systemic therapy is of interest.

The panel voted on several questions relating to patients presenting with synchronous low-burden mHSPC.

Q73: For the majority of patients with low-burden synchronous mHSPC with PSMA PET positive retroperitoneal lymph nodes, what is your treatment recommendation?

- Systemic therapy alone: 5% (5 votes)
- Systemic therapy plus RT of the primary 43% (45 votes)
- Systemic therapy plus RT of the primary and metastases-directed therapy (MDT): 49% (51 votes)
- RT of the primary and MDT without systemic therapy: 3% (3 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 92% voted in favour of systemic therapy plus RT to the primary tumour (with or without MDT).

Q74: In the majority of patients with synchronous low-burden mHSPC on conventional imaging, what is your treatment recommendation (regardless of the decision about metastases-directed therapy and regardless of the addition of docetaxel)?

- ADT alone: 0% (0 votes)
- ADT plus ARPI: 11% (12 votes)
- ADT plus RT of the primary tumour: 7% (7 votes)
- ADT plus ARPI plus RT of the primary tumour: 82% (85 votes)
- Abstain/unqualified to answer (2 votes)

Consensus in favour of ADT plus ARPI plus RT to the primary tumour

Q75: In the majority of patients with synchronous low-burden mHSPC on conventional imaging, do you recommend additional metastases-directed therapy (if technically feasible) of all lesions?

- Yes: 17% (18 votes)
- Yes, but only if no relevant additional and/or untreatable lesions confirmed by next-generation imaging: 57% (59 votes)
- No: 26% (27 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

Q76: In the majority of patients with synchronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, what is your treatment recommendation (regardless of the decision about metastases-directed therapy and regardless of the addition of docetaxel)?

- ADT ± ARPI: 3% (3 votes)
- ADT plus RT of the primary tumour ± ARPI: 88% (91 votes)
- Treat as M0: 9% (9 votes)
- Abstain/unqualified to answer (3 votes)

Consensus in favour of ADT plus RT to the primary tumour ± ARPI.

Q77: In patients with synchronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, do you recommend additional metastases-directed therapy (if technically feasible) of all lesions?

- Yes, in the majority of patients: 45% (47 votes)
- Yes, but only in selected patients: 39% (40 votes)
- No: 16% (17 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 84% voted in favour of recommending additional MDT for all lesions for either the majority of cases or for selected patients.

Q78: In patients with synchronous low-burden mHSPC on conventional imaging and if you use metastases-directed therapy, what is your recommendation regarding the duration of systemic therapy?

- Continuous lifelong treatment of ADT ± ARPI: 31% (30 votes)
- Continuous treatment of ADT ± ARPI for 2–3 years: 56% (54 votes)
- Intermittent (eg, interrupt after 6–12 months if PSA <0.2 ng/ml): 13% (12 votes)
- Abstain/unqualified to answer (including I did not vote for metastases-directed therapy or I do not use systemic therapy in this situation) (10 votes)

No consensus.

Q79: In patients with synchronous low-burden mHSPC on next-generation imaging and negative on conventional imaging and if you use metastases-directed therapy, what is your recommendation regarding the duration of systemic therapy?

- Continuous lifelong treatment of ADT ± ARPI: 17% (17 votes)
- Continuous treatment of ADT ± ARPI for 2–3 years: 65% (63 votes)
- Intermittent (eg, interrupt after 6–12 months if PSA <0.2 ng/ml): 18% (17 votes)
- Abstain/unqualified to answer (including I did not vote for metastases-directed therapy or I do not use systemic therapy in this situation) (9 votes)

No consensus.

3.3.4. Metachronous mHSPC

As outlined in Section 3.3.3, several randomised clinical trials showed that addition of an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT improved OS in comparison to ADT

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alone, regardless of disease volume (low or high) and/or the time of metastasis presentation (synchronous or metachronous) [123–127]. In general, there are fewer data on patients with metachronous mHSPC, as patients with metachronous disease were either excluded or were a minority of participants in most studies. Therefore, results for metachronous disease should be interpreted with caution.

MDT has been proposed as a means of delaying systemic treatment for patients with oligorecurrent disease [135–137]. In the phase 2 randomised STOMP trial, MDT was associated with prolongation of the time to commencement of ADT in comparison to surveillance for patients with metachronous oligorecurrent mHSPC (≤3 metastases), although the criteria for commencement of ADT were not defined in the study protocol [135]. Choline PET was used for staging in this study. In the phase 2 randomised ORIOLE trial, stereotactic ablative radiation was associated with better PFS at 6 mo in comparison to observation for patients with oligometastatic mHSPC (≤3 metastases); the number of metastases was determined via conventional imaging [136]. Combined results from STOMP and ORIOLE confirmed a significant improvement in PFS with MDT [137]. The SABR-COMET trial reported better OS with MDT in comparison to SOC, but the study population was heterogeneous (only 16% of patients had PC), making it difficult to draw any definitive conclusions from these data [138]. The EXTEND trial, which randomised 87 patients with oligometastatic PC (≤5 metastases) to intermittent ADT with or without MDT, showed improvements in PFS and eugonadal PFS in the arm with MDT [139].

The panel voted on several questions relating to patients presenting with metachronous low-burden mHSPC.

Q80: In the majority of patients with metachronous low-burden mHSPC on conventional imaging, what is your treatment recommendation?

- Systemic therapy alone: 22% (23 votes)
- Systemic therapy plus metastases directed therapy: 68% (71 votes)
- Metastases directed therapy alone: 10% (10 votes)
- Abstain/unqualified to answer (2 votes)

No consensus

A combined total of 90% voted in favour of systemic therapy as the main treatment strategy.

Q81: If you recommend systemic therapy in a patient with metachronous low-burden mHSPC on conventional imaging, what type of systemic therapy do you recommend?

- ADT alone: 8% (8 votes)
- ADT plus ARPI: 91% (94 votes)
- ARPI alone: 1% (1 vote)
- ADT plus ARPI plus docetaxel: 0% (0 votes)
- Abstain/unqualified to answer (Including I do not use systemic therapy in this situation) (3 votes)

Strong consensus in favour of ADT plus an ARPI.

Q82: If you recommend metastases-directed therapy in a patient with metachronous low-burden mHSPC on conventional imaging, what do you recommend?

- Treat based on conventional imaging: 12% (11 votes)
- Treat only if no relevant additional and/or untreatable lesions confirmed by next-generation imaging: 88% (78 votes)
- Abstain/unqualified to answer (including I do not recommend metastases directed therapy in this situation) (17 votes)

Consensus in favour of treating only if no relevant additional and/or untreatable lesions are confirmed via next-generation imaging.

Q83: In the majority of patients with metachronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, what is your treatment recommendation?

- Systemic therapy alone: 14% (15 votes)
- Systemic therapy plus metastases directed therapy: 69% (72 votes)
- Metastases directed therapy alone: 13% (13 votes)
- Monitoring and no immediate treatment: 4% (4 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 83% voted in favour of systemic therapy as the basis of treatment, and 82% voted for MDT alone or combined with systemic therapy.

It has been shown that the time of metastatic presentation and disease burden are prognostic in mHSPC and that patients with metachronous low-burden disease have the best prognosis [118,121]. Although combination therapies were continued on a lifelong basis in pivotal trials, patients with metachronous low-burden disease, who generally have better prognosis, may benefit from intermittent systemic treatment, although relevant evidence is lacking (see also Section 3.3.5 on treatment de-escalation) [140].

The panel voted on a number of questions related to the duration of systemic therapy in patients with metachronous low-burden mHSPC.

Q84: If you recommend systemic therapy alone in a patient with metachronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, what is your treatment recommendation?

- ADT alone, intermittent therapy: 6% (5 votes)
- ADT alone, continuous therapy: 5% (4 votes)
- ADT plus ARPI, intermittent therapy: 43% (34 votes)
- ADT plus ARPI, continuous therapy: 43% (34 votes)
- ARPI alone, intermittent therapy: 3% (2 votes)
- ARPI alone, continuous therapy: 0% (0 votes)
- Abstain/unqualified to answer (including I do not recommend systemic therapy alone in this situation) (27 votes)

No consensus.

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A combined total of 86% voted in favour of ADT plus an ARPI using either a continuous or an intermittent regimen.

Q85: If you recommend metastases-directed therapy in a patient with metachronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, what is your recommendation regarding systemic therapy?

- No systemic therapy: 10% (10 votes)
- Continuous lifelong treatment of ADT ± ARPI or ARPI alone: 12% (11 votes)
- Continuous treatment of ADT ± ARPI or ARPI alone for 2–3 years: 35% (34 votes)
- Intermittent ADT ± ARPI or ARPI alone (eg, interrupt after 6–12 months if PSA <0.2 ng/ml): 43% (41 votes)
- Abstain/unqualified to answer (including I do not use metastases-directed therapy) (10 votes)

No consensus.

Q86: If you recommend systemic therapy in a patient with metachronous low-burden mHSPC on conventional imaging, what is your recommendation regarding systemic therapy?

- Continuous lifelong treatment of ADT ± ARPI or ARPI alone: 51% (52 votes)
- Continuous treatment of ADT ± ARPI or ARPI alone for 2–3 years: 32% (33 votes)
- Intermittent ADT ± ARPI or ARPI alone (eg, interrupt after 6–12 months if PSA <0.2 ng/ml): 17% (18 votes)
- Abstain/unqualified to answer (including I do not recommend metastases-directed therapy or I do not use systemic therapy in this situation) (3 votes)

No consensus.

A combined total of 83% voted in favour of continuous rather than intermittent therapy.

Q87: If you recommend systemic therapy in patients with metachronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, what is your recommendation regarding systemic therapy?

- Continuous lifelong treatment of ADT ± ARPI or ARPI alone: 30% (30 votes)
- Continuous treatment of ADT ± ARPI or ARPI alone for 2–3 years: 34% (34 votes)
- Intermittent ADT ± ARPI or ARPI alone (eg, interrupt after 6–12 months if PSA <0.2 ng/ml): 36% (35 votes)
- Abstain/unqualified to answer (including I do not recommend metastases-directed therapy or I do not use systemic therapy in this situation) (7 votes)

No consensus.

3.3.5. *Treatment de-escalation*

All studies evaluating combination therapy in mHSPC used treatment with ADT + ARPI until disease progression or unacceptable toxicity [123–127]. Before the era of combination therapies, use of intermittent ADT (iADT) was considered a possible alternative to continuous ADT (cADT), especially in patients who demonstrated a good biochemical response to ADT [141,142]. Prospective trials have evaluated iADT in mHSPC, but none have shown a clear difference in OS or noninferiority with iADT versus cADT [141,142]. In the largest trial, SWOG-9346, 1535 patients with mHSPC whose PSA had decreased to ≤4 ng/ml after 7 mo of ADT were randomly assigned to receive either iADT or cADT. Median survival was 5.8 yr with cADT and 5.1 yr with iADT (HR for death with iADT, 1.10, 90% CI 0.99–1.23) [141]. The depth and kinetics of the PSA decline after ADT initiation are strong independent predictors of survival in mHSPC. For patients with mHSPC treated with ADT alone, SWOG-9346 showed that the group that reached PSA ≤0.2 ng/ml had better OS (75 mo) than the group that reached PSA 0.2–4 ng/ml (44 mo) or PSA >4 ng/ml (13 mo) [141]. In addition, more recent combination therapy trials demonstrated that a deep decline in PSA is prognostic [143–147]. Therefore, it is possible that for patients with mHSPC who reach undetectable PSA (<0.2 ng/ml) on systemic treatment, intermittent therapy or other forms of treatment de-escalation—although currently not a standard practice—may be as effective as continuous systemic therapy while conferring potential advantages, such as fewer adverse events and lower costs [140,148].

Q88: For the majority of patients with mHSPC with deep remission to systemic therapy (eg, PSA <0.2 ng/ml) and complete radiological response of measurable lesions (PCWG3 criteria), and no relevant side-effects, do you recommend treatment interruption?

- Yes, after 6–12 months: 7% (7 votes)
- Yes, after 24–36 months: 41% (41 votes)
- Yes, after >36 months: 6% (6 votes)
- No, I recommend continuous therapy: 47% (48 votes)
- Abstain/unqualified to answer (4 votes)

No consensus.

Q89: For the majority of patients with mHSPC with deep remission to systemic therapy (eg, PSA <0.2 ng/ml) and no relevant side-effects, do you discuss the option of treatment interruption?

- Yes, after 6–12 months: 14% (15 votes)
- Yes, after 24–36 months: 45% (46 votes)
- Yes, after >36 months: 15% (15 votes)
- No, I recommend continuous therapy: 26% (27 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

Intermittent therapy remains controversial. Furthermore, if combination therapy is used, it is not clear whether one or all treatments can be safely interrupted. Different approaches are being evaluated; in the EORTC De-escalate trial, both ADT and the ARPI will be suspended, whereas in the LIBERTAS trial, ADT is stopped while apalutamide is continued [140] (Table 2).

Q90: If you use treatment interruption in patients with mHSPC with deep remission to systemic therapy (eg, PSA <0.2 ng/ml), what is your recommendation regarding systemic therapy?

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Table 2 – Trials investigating de-escalation strategies in mHSPC

Study	Phase	Pts	Design	Primary endpoint	Primary completion date
DE-ESCALATE EORTC NCT05974774 Planning stage	3	1600	**mHSPC:** PSA <0.2 ng/ml after 6–12 mo on ADT + ARPI (± docetaxel ± RTPT) randomised to continued therapy versus suspension of systemic therapy **Criteria for restarting systemic therapy:** Clinical progression, radiological progression, or PSA increase to ≥50% of iPSA at diagnosis to a maximum of 5 ng/ml	OS rate at 36 mo Proportion of patients who do not restart hormonal therapy within 1 yr of interruption	09/2029
LIBERTAS Janssen Research & Development NCT05884398 Recruiting trial	3	333	**mHSPC:** ADT + APA for 6 mo followed by randomisation of pts with PSA <0.2 ng/ml to APA + cADT vs APA + iADT **Criteria for restarting ADT in the ADT suspension arm:** PSA >10 ng/ml (or return to baseline if iPSA was <10 ng/ml) PSA doubling time <6 mo New or worsening prostate cancer symptoms	18-mo radiographic PFS rate Severity of adjusted hot flash score at 18 mo	05/2027
A-DREAM Alliance for Clinical Trials in Oncology NCT05241860 Active, not recruiting	2	79	**mHSPC:** If PSA <0.2 ng/ml after 18–24 mo on ADT and at least 12 mo on ARPI, suspension of both ADT and ARPI **Criteria for restarting systemic therapy:** PSA ≥5 ng/ml Radiographic progression Prostate cancer related symptoms	Treatment-free at 18 mo in the context of a normalised testosterone	06/2024
DUOS Apa/Enza-short Recruiting status NA	2	400	**Low-volume mHSPC** ARPI for 12 mo, followed by randomisation to ARPI cessation or continuation **Criteria for restarting ARPI therapy:** If PSA ≤0.2 ng/ml at interruption, restart if PSA ≥0.3 ng/ml If PSA >0.2 ng/ml at interruption, restart in cases with a confirmed 50% rise in PSA	Clinical PFS Radiological progression (PCWG3 criteria) Development of symptoms due to cancer progression Start of a new treatment line	NA

ADT = androgen deprivation therapy; cADT = continuous ADT; iADT = intermittent ADT; APA = apalutamide; ARPI = androgen receptor pathway inhibitor; EORTC = European Organisation for Research and Treatment of Cancer; mHSPC = metastatic hormone-sensitive prostate cancer; NA = not available; OS = overall survival; PFS = progression-free survival; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; iPSA = initial PSA; Pts = patients; RTPT = radiation to the primary tumour; STx = systemic therapy.

- Suspend the ARPI: 19% (16 votes)
- Suspend ADT: 4% (3 votes)
- Suspend both ADT and the ARPI: 77% (65 votes)
- Abstain/unqualified to answer (including I did not vote for interruption) (22 votes)

Consensus in favour of recommending suspension of both ADT and the ARPI if treatment interruption is used.

Current trials evaluating treatment de-escalation use different criteria for restarting therapy, and the APCCC panel voted on this question. It is worth noting that in SWOG9346, ADT was resumed in the intermittent group when PSA rose to ≥20 ng/ml (or returned to baseline in the case of patients who had PSA <20 ng/ml before enrolment). At the discretion of investigators, treatment could be reinitiated when PSA reached 10 ng/ml or when symptoms developed [138]. The role of imaging in the oligoprogressive disease setting was also discussed.

Q91: If you use treatment interruption in patients with mHSPC with deep remission to systemic therapy (eg, PSA <0.2 ng/ml), what is your trigger to restart systemic therapy in the absence of clinical progression and in the context of recovered testosterone?

- Based on PSA rise: 13% (11 votes)
- Based on imaging with or without PSA rise: 13% (11 votes)
- Based on PSA rise or imaging progression, whichever occurs first: 74% (62 votes)
- Abstain/unqualified to answer (including I did not vote for interruption) (22 votes)

No consensus.

Q92: If you use treatment interruption in patients with mHSPC with deep remission to systemic therapy (eg, PSA <0.2 ng/ml) and if on a PSMA PET during treatment interruption oligoprogressive disease is identified, what is your recommendation in the context of recovered testosterone?

- Re-start systemic therapy: 16% (14 votes)
- Metastases-directed therapy: 27% (23 votes)
- Both of the above: 57% (49 votes)
- Abstain/unqualified to answer (including I did not vote for interruption) (20 votes)

No consensus.

Q93: For the majority of patients with mHSPC with deep remission on ADT + ARPI (eg, PSA <0.2 ng/ml) and bothersome side-effects (fatigue, cognitive decline, falls, hot flashes), what is your recommendation regarding systemic therapy?

- No change in systemic therapy: 3% (3 votes)
- ARPI dose reduction (ADT continued): 30% (30 votes)
- Suspend the ARPI (ADT continued): 22% (22 votes)
- Suspend ADT (ARPI continued): 4% (4 votes)
- Suspend both ADT and the ARPI: 41% (42 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

3.3.6. *Special situations*

To date, we have no evidence on whether to recommend a different treatment for patients with mHSPC whose tumours harbour a pathogenic *BRCA* alteration. Since recent

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studies have demonstrated the efficacy of ARPI + PARP inhibitor combinations for first-line treatment of mCRPC, it is possible that these combinations could also be effective when used earlier, in the mHSPC setting [149]. Several ongoing randomised phase 3 studies are evaluating this strategy. The AMPLITUDE trial (NCT04497844) is comparing ADT + abiraterone + niraparib versus ADT + abiraterone, while TALAPRO-3 (NCT04821622) is comparing ADT + enzalutamide + talazoparib versus ADT + enzalutamide. The primary endpoint in both trials is rPFS. Estimated primary completion dates are November 2024 for AMPLITUDE and September 2025 for TALAPRO-3. A third ongoing trial, EvoPAR-PR01 (NCT06120491), is assessing the PARP inhibitor saruparib; the estimated primary completion date is November 2028. In addition, STAMPEDE 2.0 has an arm evaluating the addition of niraparib in biomarker-positive patients. According to a World Health Organisation (WHO) pharmacovigilance analysis, there is a higher risk of myelodysplastic syndrome and acute myeloblastic leukaemia with the use of PARP inhibitors in general, and the ongoing trials in mHSPC will be closely monitored for these events [150].

It has also been reported that DNA repair defects are predictive of sensitivity to platinum agents in patients with mCRPC [151–153]. Therefore, it is possible that platinum chemotherapy could be effective in patients with mHSPC and a pathogenic *BRCA* alteration.

APCCC 2024 panellists voted on which treatment to recommend for patients with mHSPC whose tumours harbour a pathogenic *BRCA* alteration.

Q94: In patients with synchronous mHSPC and presence of a pathogenic *BRCA* alteration, does this information change your treatment recommendation for the patient?

- Yes, I recommend ADT + ARPI + docetaxel triplet systemic therapy over ADT + ARPI doublet systemic therapy regardless of disease burden: 17% (16 votes)
- Yes, I add a platinum chemotherapy to systemic therapy regardless of disease burden: 0% (0 votes)
- Yes, I add a PARP inhibitor to systemic therapy regardless of disease burden: 18% (17 votes)
- No: 65% (62 votes)
- Abstain/unqualified to answer (11 votes)

No consensus.

The presence of neuroendocrine PC (NEPC) or small-cell morphology is associated with poor outcomes [154–156]. Importantly, focal positive staining for chromogranin A, synaptophysin, or CD56 can be often found in PC; the presence of a neuroendocrine component does not always equate to NEPC, and these patients may present with widely variable pathology and prognosis.

De novo neuroendocrine tumours of the prostate can be separated into well-differentiated neuroendocrine tumours (rare) and high-grade neuroendocrine carcinomas (large- and small-cell carcinoma). Neuroendocrine markers that can help in diagnosis include synaptophysin, chromogranin, CD56, TTF1, NSE, and INSM1; however, expression of neuroendocrine markers on immunohistochemistry (IHC) is not required if the tumour shows characteristic morphological features [157].

In the WHO classification of PC, treatment-emergent NEPC (t-NEPC) in the sense of partial or complete high-grade neuroendocrine differentiation following ADT is well defined and described as a spectrum of histological features including pure neuroendocrine carcinoma, pure small-cell carcinoma, and, in rare cases, large-cell neuroendocrine carcinoma and tumours with a poorly differentiated prostate adenocarcinoma component and high-grade neuroendocrine carcinoma components (typically negative or only focal expression of the markers PSA, PAP, P501S, and NKX3.1) and typically a high Ki-67 index >80% and neuroendocrine markers, including synaptophysin, chromogranin, CD56, and newer markers such as insulinoma-associated protein 1 [158].

For patients with mCRPC (including more than 50% of patients with clinicopathological aggressive features), combination therapy with cabazitaxel + carboplatin improved PFS in a phase 1/2 trial [159]. According to the NCCN guidelines, carboplatin + cabazitaxel with G-CSF support can be considered for fit patients with aggressive-variant mCRPC [7]. So far, there is no evidence to recommend a platinum-based combination in newly diagnosed HSPC with aggressive disease features.

Q95: For the majority of patients with mHSPC, if there is histological evidence of a relevant neuroendocrine component (not pure small cell carcinoma) will it change your clinical management?

- Yes, I recommend docetaxel as part of the initial treatment regimen: 28% (27 votes)
- Yes, I recommend a platinum (± taxane) as part of the initial treatment regimen: 44% (42 votes)
- No: 28% (27 votes)
- Abstain/unqualified to answer (10 votes)

No consensus.

3.3.7. *RT to the primary tumour in mHSPC*

As discussed previously, for patients with low-burden disease, addition of RT to the primary tumour to ADT improved OS in comparison to ADT alone in a prespecified and prepowered subgroup analysis of STAMPEDE, but not in HORRAD or PEACE-1 [115,128–130]. In PEACE-1, addition of RT to the primary tumour to SOC ± abiraterone improved rPFS but not OS in the low-burden population [115,130]. RT to the primary tumour seemed to improve the time to serious genitourinary events in the low-volume group and the overall population. Details of serious genitourinary events were reported only for the low-burden population and included receipt of a urinary catheter or double-J stent, nephrostomy, prostate RT, TURP, and RP, with a major difference observed for prostate RT and TURP. The authors concluded that on the basis of these results, RT to the primary tumour may also be considered in selected patients with high-burden disease, but data for this subgroup have not yet been reported or published [130]. Different RT regimens were used in the different trials (HORRAD, STAMPEDE, PEACE-1), resulting in different biological equivalent

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doses [115,128–130,160]. In the most recent trial, PEACE-1, a conventional radiation dose of 74 Gy to the prostate did not confer an OS benefit, even for patients with low-burden mHSPC [115,130].

The APCCC panel voted on the recommended radiation dose for patients with mHSPC who receive RT to the primary tumour.

Q96: In patients with high-volume synchronous mHSPC without relevant local symptoms, do you recommend local radiation therapy of the primary in addition to systemic therapy?

- Yes, in the majority of patients: 9% (10 votes)
- Yes, but only in selected patients: 24% (25 votes)
- No, I usually do not recommend RT in this situation: 67% (70 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

A combined total of 91% voted against recommending RT to the primary tumour for the majority of patients with high-volume mHSPC.

Q97: In patients with low-volume synchronous mHSPC without relevant local symptoms that receive ADT plus an ARPI, do you recommend local radiation therapy of the primary in addition to systemic therapy?

- Yes, in the majority of patients: 87% (91 votes)
- Yes, but only in selected patients: 11% (12 votes)
- No, I usually do not recommend RT in this situation: 2% (2 votes)
- Abstain/unqualified to answer (1 vote)

Consensus in favour of recommending local RT to the primary tumour in addition to systemic therapy in the majority of patients.

Q98: For the majority of patients with synchronous mHSPC who are planned for local radiation therapy, what is your recommended radiation schedule?

- A dose escalated RT dose, eg, 74–80 Gy in 37–40 fractions (or equivalent hypofractionated schedules such as 60–70 Gy in 20–28 fractions or ultrahypofractionation in 5 fractions): Full definitive dosing as used in localised prostate cancer: 51% (39 votes)
- A lower RT dose, eg, 55 Gy in 20 fractions or 36 Gy in six fractions as used in STAMPEDE: 49% (38 votes)
- Abstain/unqualified to answer (including I do not decide on radiation prescription schedules) (29 votes)

No consensus.

3.3.8. *Discussion on mHSPC*

Supplementary Figure 3 provides graphical representations of the voting results for questions on mHSPC.

There is a need for consistency in the terminology we use for various PC disease states and drug treatment classes. The panel did not reach consensus on these points. However, a majority voted to use the term ARPI; we note that consistent use of this term in presentations and publications may help to avoid the confusion that can occur, especially among non-experts, when several different terms are used to refer to the same group of drugs (ie, abiraterone, apalutamide, darolutamide, and enzalutamide). The same is true for the expression "hormone-sensitive PC" (HSPC), which also was chosen by a majority of panellists.

In recent years, mHSPC treatment has been revolutionised by novel therapies and the introduction of triplet systemic combination therapies (ADT + ARPI + docetaxel). It has been shown that the latter improve OS in comparison to doublet systemic therapy consisting of ADT + docetaxel. To date, however, we do not know which patients will benefit the most from triplet therapy, for which patients docetaxel can be omitted, or whether triplet therapy is superior to doublet systemic therapy with ADT + ARPI [117]. Panellists reached consensus against recommending systemic triplet therapy for patients with metachronous low-burden mHSPC, which is consistent with a recent meta-analysis showing no benefit from addition of docetaxel alone to ADT in this setting [121]. For patients with high-burden mHSPC, 54% of panellists would recommend systemic triplet for the majority of patients, and 40% would recommend it for selected patients. For most panellists, the most important factor when recommending triplet therapy seemed to be volume of disease rather than timing of disease or patient age. For the less common situation of metachronous high-burden disease, 34% of panellists voted to recommend systemic triplet therapy for the majority of patients, and 50% recommended this for selected patients only.

Panellists reached consensus in favour of recommending addition of RT to the primary tumour to systemic therapy for patients with low-volume synchronous mHSPC, independent of the type of imaging used for staging. However, there was no consensus on the preferred duration of systemic treatment, or whether to give systemic therapy on a continuous or intermittent basis. Despite a lack of strong supporting evidence, there was considerable endorsement of MDT addition when managing low-volume synchronous mHSPC. Nonetheless, voting differed according to the type of imaging used: 17% of panellists voted to use MDT for the majority of patients with synchronous low-burden mHSPC on conventional imaging, while 45% voted for MDT for patients staged via next-generation imaging. Large randomised trials are under way that will generate relevant data on these questions; interestingly, there does not seem to be a problem in accruing patients to these studies, even though some will not be randomised to receive MDT.

For patients with metachronous oligometastatic PC, there are more data indicating that MDT may improve clinical outcomes than for the synchronous disease setting. Nonetheless, there are as yet no large randomised trials showing an OS benefit of MDT in the metachronous oligometastatic setting. At APCCC 2024, the majority of panellists voted to recommend addition of systemic therapy to MDT for these patients. For patients with low-burden metachronous mHSPC, the type of imaging used for staging made a difference: for patients staged via conventional imaging, only 10% of panellists voted for MDT alone, but for patients staged via next-generation imaging, 13% of panellists voted for MDT alone and another 4% voted for monitoring with no immediate therapy. In addition, more panellists were in

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favour of intermittent (vs continuous) therapy if metachronous low-burden mHSPC was detected via next-generation imaging than when detected via conventional imaging. A relevant question is what the goal of MDT addition to systemic therapy is. At APCCC 2019, the panel voted on treatment goals for patients with oligometastatic disease in general when recommending MDT instead of systemic therapy; in all, 81% voted that the goal was to delay the start of ADT, to prolong PFS, to prolong OS, or a combination of these. The 2019 panel also voted on the goal of treatment when recommending MDT plus systemic therapy; in all, 85% voted for prolongation of PFS, OS, or both [2]. For oligometastatic PC, we have no strong data on the effect of combining MDT with systemic treatments and, if so, which treatments to use and for how long. This was reflected by a failure to reach consensus on any of these questions. Trials are ongoing that will help in answering at least some of them.

Regarding de-escalation of therapy, the panel was split in half on whether or not to recommend de-escalation for patients with a deep response to treatment. There was also no consensus on whether and when to at least discuss the option of discontinuing systemic therapy. However, when de-escalating therapy, panellists reached consensus in favour of stopping both ADT and the ARPI, rather than only one or the other. Several planned or ongoing trials will help in addressing this important question [140] (Table 2).

The majority of panellists voted that the presence of a pathogenic *BRCA* alteration would not change their treatment recommendation in the mHSPC setting, whereas NEPC presence would.

As these results show, the field of mHSPC treatment remains complex and will be a fruitful area for future research and consensus meeting discussions.

3.4. mCRPC

3.4.1. General questions

Single-agent PARP inhibitors are a standard treatment for patients with mCRPC who progress on an ARPI and exhibit selected homologous recombination repair (HRR) gene alterations [7,73]. Olaparib as monotherapy is approved in Europe for patients with mCRPC with germline and/or somatic alterations in *BRCA1* or *BRCA2* genes. In the USA, approval of olaparib as monotherapy for mCRPC after progression on an ARPI includes patients with 14 HRR gene alterations on the basis of findings from the PROFOUND trial [161]. Similarly, the PARP inhibitor rucaparib is approved in the USA for treatment of patients with mCRPC with deleterious germline or somatic *BRCA1/2* alterations on the basis of results from the TRITON-2 and TRITON-3 trials [162,163]. Results from the randomised PROpel, MAGNITUDE, and TALAPRO-2 trials have been published since APCCC 2022 [164–169]. PROpel met its primary endpoint: olaparib plus abiraterone improved rPFS in comparison to abiraterone alone in the first-line setting for biomarker-unselected patients with mCRPC [164,165]. Alterations in selected HRR genes (Supplementary Table 1) were determined after randomisation but before primary analysis via a solid (FoundationOne CDX) and/or a circulating tumour (ct)DNA–based (FoundationOne Liquid CDx) assay. For patients whose cancers had alterations in at least one of the selected HRR genes, particularly those with *BRCA* alterations, the combination of olaparib plus abiraterone improved OS, which was a secondary endpoint. An OS improvement was not observed in the overall population (although by the third data cutoff, there was a positive OS trend that favoured the combination) [164,165]. On the basis of these data, the US Food and Drug Administration (FDA) approved the olaparib + abiraterone combination only for patients with pathogenic *BRCA* alterations. Conversely, the European Medicines Agency (EMA) approved this combination for all patients with mCRPC, irrespective of genomic findings.

In the MAGNITUDE trial, niraparib plus abiraterone improved the primary endpoint of rPFS in comparison to abiraterone alone in patients with mCRPC harbouring defects in at least one of nine HRR genes [166,167] (Supplementary Table 1). HRR status was determined before randomisation using one of several solid tumour and ctDNA assays, including accredited local laboratory biomarker tests. A preplanned futility analysis for tumours without evidence of HRR gene alterations for this combination showed no benefit, and the trial subsequently focused on recruiting only patients whose tumours had HRR defects. At the second prespecified interim analysis, niraparib plus abiraterone did not demonstrate a benefit in OS in comparison to abiraterone alone in patients with *BRCA1/2* alterations [166,167]. It is noteworthy that there was relevant crossover to the PARP inhibitor (PARPi) arm in MAGNITUDE (34% to PARPi and 9% to platinum chemotherapy), which may affect the OS benefit observed [170]. On the basis of these data, the FDA and EMA approved the combination of niraparib + abiraterone only for patients with mCRPC who have pathogenic *BRCA* alterations.

Finally, TALAPRO-2 showed that the combination of talazoparib plus enzalutamide prolonged rPFS (the primary endpoint) in the overall cohort, with the greatest benefit observed for patients with evidence of alterations in at least one of 12 HRR genes [168,169] (Supplementary Table 1). In this trial, HRR status was determined before randomisation using a FoundationOne CDx and/or FoundationOne Liquid CDx assay. The OS data are still immature [168,169]. The FDA approved this combination for patients with mCRPC who have evidence of HRR gene alterations, while the EMA approved the combination for all patients with mCRPC.

In two additional first-line mCRPC trials, CONTACT-02 (atezolizumab + cabozantinib vs ARPI switch) and PSMAfore (^{177}Lu-PSMA vs ARPI switch), it has been reported that both the atezolizumab + cabozantinib combination and ^{177}Lu-PSMA met the primary endpoint of improving rPFS, but did not improve OS, in comparison to an ARPI switch [171,172]. However, the results from these studies have not been published at the time of writing.

The PRESIDE trial, which evaluated the benefit of continuing enzalutamide beyond progression in the mCRPC setting and adding docetaxel versus stopping enzalutamide and giving docetaxel alone, also met its primary endpoint, showing a statistically significant but clinically modest improvement of approximately 2 mo in PFS and PSA-

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based endpoints, with no impact on OS or patient-reported outcomes [173]. Of note, a PSA decline ≥50% with docetaxel was achieved in only 25% of patients in this trial (vs 45% in TAX327). With all the caveats for cross-trial comparisons, these data raise concerns that docetaxel may be less active in the second-line setting when sequenced after a prior ARPI.

The APCCC panel addressed a number of questions related to PARP inhibition in patients with advanced PC and the sequencing of therapies in light of the many options that are now available for patients with mCRPC.

Q104: Do you recommend somatic genetic testing for DDR genes before recommending a PARP inhibitor and ARPI combination treatment for first-line mCRPC?

- Yes: 95% (98 votes)
- No 5% (5 votes)
- Abstain/unqualified to answer (3 votes)

Strong consensus in favour of somatic genetic testing for alterations in DNA damage repair (DDR) genes before recommending a PARPi.

Of note, the dose of the talazoparib + enzalutamide combination was required was lower than the monotherapy dose recommended on the basis of pharmacokinetic drug-drug interaction studies of the PARPi [168,169]. The panel voted on whether it is appropriate to use any combination of an ARPI with a PARPi.

Q105: If you use a combination of ARPI plus PARP inhibitor, is it appropriate to combine any ARPI with any PARP inhibitor for first-line mCRPC?

- Yes: 29% (28 votes)
- No: 71% (68 votes)
- Abstain/unqualified to answer (10 votes)

No consensus.

CONTACT-02 is a phase 3 trial comparing cabozantinib + atezolizumab versus an ARPI switch in patients with mCRPC; results were presented at ASCO GU 2023 [171]. The trial met the primary endpoint of rPFS, demonstrating a statistically significant but clinically modest improvement of 6.3 mo versus 4.2 mo. The combination had not been approved by any regulatory agency at the time of voting or the time of writing. The panel voted on this combination for patients progressing on or after an ARPI in the context of other available options.

Q106: In the majority of patients with mCRPC progressing on ADT plus an ARPI (either started for mHSPC or CRPC), do you recommend cabozantinib and atezolizumab if they are fit for chemotherapy or ^{177}Lu-PSMA therapy?

- Yes: 8% (8 votes)
- No: 92% (88 votes)
- Abstain/unqualified to answer (10 votes)

Strong consensus against recommending cabozantinib and atezolizumab for the majority of patients.

3.4.2. Sequencing of treatment options: no tumour genomic profiling available or no evidence of DDR alterations on tumour genomic profiling

The APCCC 2024 panel voted on their preferred first-line mCRPC treatment option for patients who had received ADT ± docetaxel for mHSPC. The same question was asked twice, for (1) patients without tumour genomic profiling and (2) patients with no alterations in DDR genes according to tumour genomic profiling. Patients with rapid progression from mHSPC to mCRPC (based on the treatment received in mHSPC) were not addressed at APCCC 2024, although the panel voted on that question at APCCC 2022 [5].

Q107: For the majority of patients with mCRPC with somatic genetic testing not available, what is your treatment recommendation in the first-line setting when they received ADT (±docetaxel) for mHSPC?

- ARPI: 84% (84 votes)
- ARPI plus PARP inhibitor: 11% (11 votes)
- Other option, eg, taxane or ^{177}Lu-PSMA therapy according to appropriate treatment criteria: 5% (5 votes)
- Abstain/unqualified to answer (6 votes)

Consensus in favour of an ARPI in patients with first-line mCRPC after ADT ± docetaxel and no somatic genetic testing.

Q110: For the majority of patients with mCRPC who have been tested and no DDR alteration was identified, what is your treatment recommendation in the first-line setting when they received ADT (±docetaxel) for mHSPC?

- ARPI: 84% (83 votes)
- ARPI plus PARP inhibitor: 7% (7 votes)
- Other option, eg, taxane or ^{177}Lu-PSMA therapy according to appropriate treatment criteria: 9% (9 votes)
- Abstain/unqualified to answer (7 votes)

Consensus in favour of an ARPI in patients with first-line mCRPC after ADT ± docetaxel and no DDR gene alterations.

Despite practice-changing findings from clinical trials, real-world data suggest that the uptake of treatment combinations in mHSPC has been slowed by delays in education and accessibility [174,175]. However, it is likely that the majority of patients with mHSPC will receive systemic doublet or triplet therapy with or without RT to the primary tumour and ADT in the future.

The APCCC 2024 panel voted on their preferred first-line mCRPC option for patients who had received ADT plus an ARPI for mHSPC. The same question was asked twice, for (1) patients without tumour genomic profiling and (2) patients with no alterations in DDR genes according to tumour genomic profiling.

Q108: For the majority of patients with mCRPC and somatic genetic testing not available, what is your treatment recommendation in the first-line setting when they received ADT+ARPI for mHSPC?

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- Alternate ARPI: 5% (5 votes)
- Add PARP inhibitor to current therapy or change to alternate ARPI plus PARP inhibitor: 2% (2 votes)
- Docetaxel: 85% (84 votes)
- Radium-223: 1% (1 vote)
- ^{177}Lu-PSMA: 7% (7 votes)
- Abstain/unqualified to answer (7 votes)

Consensus in favour of docetaxel in patients with first-line mCRPC after ADT + ARPI without somatic genetic testing.

Q111: For the majority of patients with mCRPC who have been tested and no DDR alteration was identified, what is your treatment recommendation in the first-line setting when they received ADT+ ARPI for mHSPC?

- Alternate ARPI: 4% (4 votes)
- Add PARP inhibitor to current therapy or change to alternate ARPI plus PARP inhibitor: 1% (1 vote)
- Docetaxel: 88% (87 votes)
- Radium-223: 1% (1 vote)
- ^{177}Lu-PSMA: 6% (6 votes)
- Abstain/unqualified to answer (7 votes)

Consensus in favour of docetaxel in patients with first-line mCRPC after ADT + ARPI and no DDR gene alterations.

Triplet therapy is a standard systemic option in mHSPC on the basis of data from the PEACE-1 and ARASENS trials [115,116]. The APCCC 2024 panel voted on their preferred first-line mCRPC option for patients who had received ADT plus an ARPI plus docetaxel for mHSPC. The same question was asked twice, for (1) patients without tumour genomic profiling and (2) patients with no alterations in DDR genes according to tumour genomic profiling.

Q109: For the majority of patients with mCRPC and somatic genetic testing not available, what is your treatment recommendation in the first-line setting when they received ADT + ARPI and docetaxel for mHSPC?

- Alternate ARPI: 4% (4 votes)
- Add PARP inhibitor to current therapy or change to alternate ARPI plus PARP inhibitor: 4% (4 votes)
- Taxane: 19% (19 votes)
- Radium-223: 0% (0 votes)
- ^{177}Lu-PSMA: 73% (72 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

Q112: For the majority of patients with mCRPC who have been tested and no DDR alteration was identified, what is your treatment recommendation in the first-line setting when they received ADT+ ARPI + docetaxel for mHSPC?

- Alternate ARPI: 5% (5 votes)
- Add PARP inhibitor to current therapy or change to alternate ARPI plus PARP inhibitor: 1% (1 vote)
- Taxane: 19% (19 votes)
- Radium-223: 0% (0 votes)
- ^{177}Lu-PSMA: 75% (74 votes)
- Abstain/unqualified to answer (7 votes)

Consensus in favour of ^{177}Lu-PSMA in patients with first-line mCRPC after ADT + ARPI + docetaxel and no DDR gene alterations.

3.4.3. mCRPC tumour genetic profiling: non-BRCA2 DDR alterations

Differences in baseline prognostic factors, HRR gene panels, and genomic sequencing platforms across trials (Supplementary Table 1), the sometimes scarce in-depth information in sequencing reports, variations in regulatory approval in different global regions, and the uncertain relevance of the combination with an ARPI can make clinical PARPi use confusing. This is an even greater challenge when it comes to alterations in genes other than *BRCA*, given the limited number of patients with such alterations within and across trials, with some HRR aberrations only represented in a single trial.

A recently published pooled analysis by the FDA concluded that ARPI + PARPi combinations seem to exhibit the greatest antitumour activity in patients with pathogenic alterations in *BRCA1*, *BRCA2*, *CDK12*, and *PALB2* genes [176]. In patients with *ATM* alterations, the overall response rate (ORR) to PARPi monotherapy was only 7% [176]. Evidence from the TOPARP-B trial suggests that *ATM* alterations are often not associated with biallelic loss, and that loss of ATM protein expression as detected on IHC might be a better predictor of benefit from olaparib [177]. This may explain the low ORR for patients with pathogenic *ATM* alterations on next-generation sequencing. In the TRITON-3 trial, which randomised patients 2:1 to receive rucaparib or a physician's choice of control therapy (docetaxel or ARPI), an exploratory analysis for the subgroup of patients with an *ATM* alteration identified a similar rPFS and no objective responses in the rucaparib and control groups. In addition, *CHEK2* alterations were associated with lack of responses or benefits to/from PARPi or ARPI + PARPi combinations [158].

The APCCC 2024 panel voted on the use of PARPi agents (alone or in combination with an ARPI) for each individual non-*BRCA* HRR alteration, and on the timing of their use relative to *BRCA2* alterations, for which the strongest data are available (Fig. 1 also shows the panellists' responses).

Q113: In the majority of patients with mCRPC and a pathogenic *ATM* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 28% (25 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 41% (36 votes)
- No 31% (27 votes)
- Abstain/unqualified to answer (18 votes)

No consensus.

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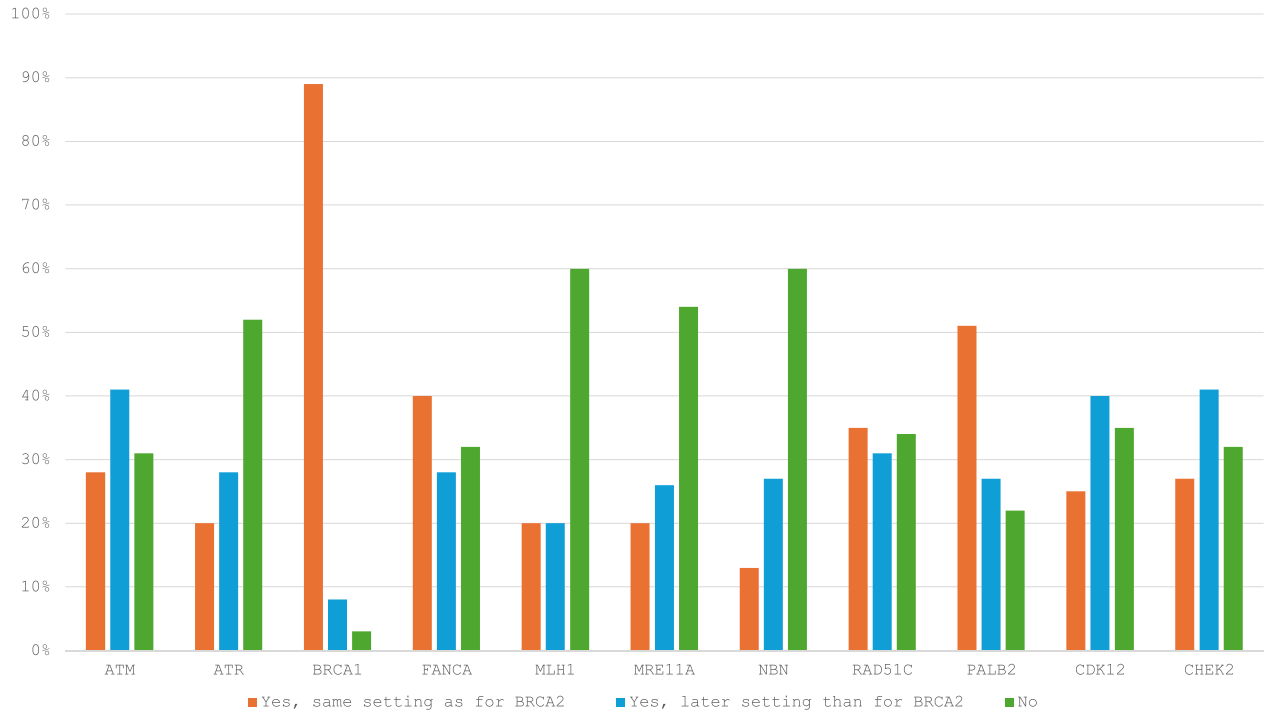

Fig. 1 – Panellist recommendations on the use of PARP inhibitor therapy according to the presence of gene alterations.

Q114: In the majority of patients with mCRPC and a pathogenic *ATR* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 20% (17 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 28% (23 votes)
- No: 52% (44 votes)
- Abstain/unqualified to answer (22 votes)

No consensus.

Q115: In the majority of patients with mCRPC and a pathogenic *BRCA1* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 89% (84 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 8% (7 votes)
- No: 3% (3 votes)
- Abstain/unqualified to answer (12 votes)

Consensus in favour of recommending a PARPi in patients with a pathogenic *BRCA1* alteration for the same indications as for a pathogenic *BRCA2* alteration.

Q116: In the majority of patients with mCRPC and a pathogenic *FANCA* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 40% (34 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 28% (24 votes)
- No: 32% (27 votes)
- Abstain/unqualified to answer (21 votes)

No consensus.

Q117: In the majority of patients with mCRPC and a pathogenic *MLH1* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 20% (17 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 20% (17 votes)
- No: 60% (51 votes)
- Abstain/unqualified to answer (21 votes)

No consensus.

Q118: In the majority of patients with mCRPC and a pathogenic *MRE11A* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 20% (16 votes)

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- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 26% (21 votes)
- No: 54% (43 votes)
- Abstain/unqualified to answer (26 votes)

No consensus.

Q119: In the majority of patients with mCRPC and a pathogenic *NBN* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 13% (10 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 27% (20 votes)
- No: 60% (45 votes)
- Abstain/unqualified to answer (31 votes)

No consensus.

Q120: In the majority of patients with mCRPC and a pathogenic *RAD51C* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 35% (29 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 31% (26 votes)
- No: 34% (28 votes)
- Abstain/unqualified to answer (23 votes)

No consensus.

Q121: In the majority of patients with mCRPC and a pathogenic *PALB2* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 51% (43 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 27% (23 votes)
- No: 22% (18 votes)
- Abstain/unqualified to answer (22 votes)

No consensus.

A combined total of 78% voted in favour of recommending a PARPi either for the same indications or at least at a later disease stage as for patients with a *BRCA2* alteration.

Q122: In the majority of patients with mCRPC and an inactivating *CDK12* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 25% (22 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 40% (35 votes)
- No: 35% (30 votes)
- Abstain/unqualified to answer (19 votes)

No consensus.

Q123: In the majority of patients with mCRPC and a pathogenic *CHEK2* alteration, do you recommend treatment with a PARP inhibitor (monotherapy or combination with ARPI depending on where the patient is in the course of the disease)?

- Yes, in the same indication as for patients with *BRCA2* alteration: 27% (23 votes)
- Yes, but at a later stage of the disease compared to patients with *BRCA2* alteration: 41% (35 votes)
- No: 32% (27 votes)
- Abstain/unqualified to answer (21 votes)

No consensus.

There is limited evidence indicating some activity of checkpoint inhibitors in patients with *CDK12* alterations on the basis of an elevated neoantigen burden [178–182].

Q124: In patients with mCRPC progressing on or after an ARPI and with an inactivating *CDK12* alteration, do you recommend treatment with a checkpoint inhibitor in preference to a standard mCRPC option?

- Yes: 25% (21 votes)
- Yes, but only if also TMB-high: 34% (29 votes)
- No: 41% (35 votes)
- Abstain/unqualified to answer (21 votes)

No consensus.

3.4.4. mCRPC tumour genetic profiling with evidence of a BRCA2 alteration

Three randomised phase 3 trials, PROpel, MAGNITUDE, and TALAPRO-2, evaluated PARPi therapies in patients with mCRPC with minimal prior exposure to treatments other than ADT [164–169]. In PROpel and TALAPRO-2, crossover of patients in the control arm to the PARPi arm was not allowed, while a significant proportion of patients in the control arm of in MAGNITUDE received either a PARPi or platinum-based therapy on progression. At ASCO GU 2024, investigators reported results from the BRCAway trial, a randomised phase 2 study of abiraterone, olaparib, or abiraterone + olaparib in patients with mCRPC and evidence of HRR alterations The trial enrolled approximately 20 patients in each arm. In the combined cohort of patients with *BRCA1/2* or *ATM* alterations, abiraterone + olaparib resulted in longer PFS in comparison to either agent given alone or sequentially, suggesting a benefit from the upfront combination. Although crossover was planned as part of the trial, only 25% of patients on olaparib monotherapy and 38% of patients on abiraterone monotherapy crossed over to the alternative treatment [183].

The evolving mHSPC landscape suggests that an increasing number of patients now receive an ARPI in the mHSPC setting, which affects first-line treatment selection when

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patients develop mCRPC. Consequently, the APCCC 2024 panel addressed the selection of first-line treatment for mCRPC, particularly for patients with evidence of pathogenic *BRCA2* alterations and taking into consideration whether they had previously received ADT ± docetaxel, ADT + ARPI, or ADT + ARPI + docetaxel in the mHSPC setting.

Q125: For the majority of patients with mCRPC with a pathogenic alteration in *BRCA2*, what is your treatment recommendation in the first-line mCRPC setting when they received ADT (±docetaxel) for mHSPC?

- ARPI: 8% (8 votes)
- ARPI plus PARP inhibitor: 92% (90 votes)
- Other option, eg, taxane or ^{177}Lu-PSMA therapy according to appropriate treatment criteria: 0% (0 votes)
- Abstain/unqualified to answer (8 votes)

Strong consensus in favour of ARPI + PARPi in patients with first-line mCRPC and a pathogenic *BRCA2* alteration.

Q126: For the majority of patients with mCRPC with a pathogenic alteration in *BRCA2*, what is your treatment recommendation in the first-line mCRPC setting when they received ADT+ ARPI for mHSPC?

- Alternate ARPI: 0% (0 votes)
- Add PARP inhibitor to current therapy or change to alternate ARPI plus PARP inhibitor: 44% (43 votes)
- PARP inhibitor monotherapy: 49% (48 votes)
- Other treatment options including: docetaxel, radium-223 or ^{177}Lu-PSMA therapy: 7% (7 votes)
- Abstain/unqualified to answer (8 votes)

No consensus.

Q127: For the majority of patients with mCRPC with a pathogenic alteration in *BRCA2*, what is your treatment recommendation in the first-line mCRPC setting when they received ADT+ ARPI + docetaxel for mHSPC?

- Alternate ARPI: 0% (0 votes)
- Add PARP inhibitor to current therapy or change to alternate ARPI plus PARP inhibitor: 41% (40 votes)
- PARP inhibitor monotherapy: 55% (54 votes)
- Other treatment options including: taxane, radium-223 or ^{177}Lu-PSMA therapy: 4% (4 votes)
- Abstain/unqualified to answer (8 votes)

No consensus.

A recently published pan-cancer study identified microsatellite instability-high (MSI-high) status in 12.8% of patients with *BRCA1* alterations and 3.4% of patients with *BRCA2* alterations. In the cohort, two patients with PC harbouring both *BRCA* alterations and MSI-high were resistant to PARPi therapy but sensitive to checkpoint inhibition [184]. The authors hypothesised that most *BRCA* alterations that coexist with MSI may be passenger alterations or bystander events and therefore do not sensitise to PARPi.

The panel voted on a question (Q128) on management of patients with evidence of MSI-high status and a *BRCA* alteration that was not well phrased and was therefore deleted.

For situations in which access to PARPi therapy is not available for patients with a pathogenic *BRCA2* alteration, there are limited clinical trial data on the efficacy of platinum-based treatments. A small phase 2 trial was stopped early because of lack of activity of carboplatin in heavily pretreated patients with mCRPC and evidence of HRR alterations [185]. Another phase 2 trial is currently ongoing [186]. While retrospective series have reported some activity of platinum-based chemotherapy in patients with HRR alterations, the platinum treatment was mostly used late in the disease trajectory after exhaustion of established standard therapies [151,187].

Q129: In patients with a confirmed pathogenic *BRCA2* alteration (germline/somatic or somatic alone) and in the case where you do not have access to a PARP inhibitor, do you recommend treatment with a platinum-based therapy instead (monotherapy or combination)?

- Yes, before a taxane chemotherapy: 49% (44 votes)
- Yes, but only after a taxane chemotherapy: 48% (44 votes)
- No: 3% (3 votes)
- Abstain/unqualified to answer (15 votes)

No consensus.

3.4.5. *ARPI switching*

The antitumour activity of sequential ARPI therapy is generally low, as demonstrated by prospective trials investigating this question and by the control arm of numerous trials [161,171,172,188,189]. For this reason, international guidelines state that an ARPI switch should be avoided because of known cross-resistance and the availability of other treatments [6,7].

In the randomised PLATO trial, patients with mCRPC who had PSA progression while on enzalutamide monotherapy did not experience any clinically meaningful benefits from either adding or switching to abiraterone [190]. It is worth noting that the analysis excluded patients who had a prolonged response to enzalutamide (17%). The results of a multicentre, single-arm, open-label study investigating sequencing of enzalutamide after abiraterone suggested some degree of antitumour activity in certain patients whose mCRPC had progressed after at least 24 wk on abiraterone [191]. In three phase 3 trials (CARD, PROfound, and CONTACT-02), an ARPI switch in the "control" arms did not generally result in clinically meaningful antitumour activity [161,171,172,189]. In the PSMAfore trial, an ARPI switch in the control arm resulted in median rPFS of almost 6 mo; this study selected asymptomatic patients with more indolent disease via inclusion and exclusion criteria (eg, patients with evidence of AR-V7 or *BRCA* alterations were excluded) who had to be considered candidates for an ARPI switch by the treating investigator. The median rPFS in the study control arm shows the importance of patient selection criteria and suggests that an ARPI switch, particularly if crossover is allowed, may be an acceptable control treatment in some trials if patients are carefully selected and thoroughly informed about other treatment options [167].

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The APCCC 2024 panel voted on three questions related to an ARPI switch either directly (one after the other) or at any time in the treatment sequence:

Q130: Do you recommend a direct switch to abiraterone in patients whose cancer is progressing on an AR antagonist (Apa/Daro/Enza)?

- Yes, in the majority of patients: 4% (4 votes)
- Yes, but only in selected patients: 30% (30 votes)
- No: 66% (67 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

Q131: Do you recommend a direct switch to an AR antagonist (Apa/Daro/Enza) in patients whose cancer is progressing on abiraterone?

- Yes, in the majority of patients: 6% (6 votes)
- Yes, but only in selected patients: 47% (48 votes)
- No: 47% (48 votes)
- Abstain/unqualified to answer (4 votes)

No consensus.

Q132: Do you recommend an alternate ARPI as monotherapy anytime in the treatment sequence in patients who have received a prior ARPI treatment?

- Yes, in the majority of patients: 5% (5 votes)
- Yes, but only in selected patients: 53% (54 votes)
- No: 42% (42 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

3.4.6. *Oligoprogressive mCRPC*

The concept of oligoprogressive disease in advanced PC is not well defined, and evidence on MDT to oligoprogressing sites in the mCRPC setting is limited [192–196].

The panel voted on a question related to their recommendation for patients with mCRPC who have multiple metastases but only one to three that are progressing according to imaging results.

Q133: For the majority of patients with multiple metastases and only oligoprogressive mCRPC (max. 3 progressing lesions), what do you recommend?

- Switch systemic therapy: 30% (31 votes)
- Switch to another systemic therapy and perform MDT of all progressing lesions: 21% (22 votes)
- Do not change systemic therapy; perform MDT of all progressing lesions: 49% (50 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

The recently published randomised phase 2 ARTO trial included 157 patients with oligometastatic CRPC (defined as $\leq$3 nonvisceral metastases) staged, for the most part, via choline PET/CT imaging [197]. Patients were randomised to receive abiraterone with or without MDT using stereotactic RT to all metastatic sites. The primary endpoint was biochemical response, and both the PSA response rates and rPFS were improved with MDT addition to abiraterone [197].

The APCCC 2024 panel voted on their treatment recommendation for first-line mCRPC with oligometastatic disease.

Q134: For the majority of patients with oligometastatic first-line mCRPC (max. 3–5 lesions), what do you recommend?

- Add/switch systemic therapy: 41% (42 votes)
- Add/switch systemic therapy and perform MDT of all lesions: 45% (46 votes)
- Perform MDT of all lesions alone: 14% (15 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

3.4.7. *Prophylactic RT in mCRPC*

A recently published phase 2 trial enrolled 78 patients with high-risk bone metastases, 17 (21.8%) of whom had advanced PC, to investigate the role of prophylactic RT to high-risk bone metastases in comparison to SOC [198]. High-risk bone lesions were defined as (1) a bulky site of disease in bone ($\geq$2 cm); (2) disease involving the hip (acetabulum, femoral head, and femoral neck), shoulder (acromion, glenoid, and humeral head), or sacroiliac joints; (3) disease in long bones occupying one-third to two-thirds of the cortical thickness (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpals, and phalanges); and (4) disease in vertebrae of the junctional spine (C7–T1, T12–L1, and/or L5–S1) and/or disease with a posterior element involvement. There was a lower rate of skeletal-related events (SREs) at 12 mo in the intervention arm than in the SOC arm (1.6% vs 29%). The trial also reported an improvement in median OS, which was a secondary endpoint [198].

Q135: For the majority of asymptomatic patients with mCRPC with progressing high-risk bone lesions, do you recommend prophylactic radiation therapy to reduce the risk of SRE?

- Yes, in the majority of patients: 36% (37 votes)
- Yes, but only in selected patients: 47% (48 votes)
- No: 17% (18 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

A combined total of 83% voted in favour of recommending prophylactic RT to patients with progressing high-risk bone lesions, at least in selected patients.

Findings from the randomised phase 3 PROMPTS trial were recently published; in this study, patients with mCRPC and asymptomatic spinal metastases were randomly assigned to either observation alone or screening spinal MRI, with pre-emptive treatment (either RT or surgical decompression) if radiographic evidence of asymptomatic spinal cord compression (SCC) was identified [199]. The primary objective was to assess the time to and incidence of confirmed clinical SCC. The occurrence of clinical SCC was minimal in both study arms (6.7% in the control group and 4.3% in the intervention group). Consequently, the

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researchers concluded that routine screening and pre-emptive treatment might not be necessary for patients with asymptomatic spinal metastases [199]. However, they suggested vigilance in these patients and recommended a low threshold for recommending spinal MRI if patients develop new back pain.

The APCCC 2024 panel voted on a question concerning patients with progressive mCRPC that includes epidural soft-tissue disease.

Q136: For the majority of asymptomatic patients with mCRPC with disease progression in the spine with epidural soft tissue component, do you recommend prophylactic radiation therapy to reduce the risk of symptomatic spinal cord compression?

- Yes, in the majority of patients: 65% (67 votes)
- Yes, but only in selected patients: 33% (34 votes)
- No: 2% (2 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

A combined total of 98% voted in favour of recommending prophylactic RT for progression of spine lesions with an epidural soft-tissue component, at least in selected patients.

3.4.8. *Discussion on mCRPC*

Supplementary Figure 4 provides graphical representations of the voting results for questions on mCRPC.

The therapeutic landscape for mCRPC is constantly evolving as new treatment options are introduced [200]. In addition, therapeutic choices in the mCRPC setting are highly influenced by treatment(s) the patient received in the mHSPC setting and by the results of genomic evaluations [201]. For most patients for whom somatic genomic testing is not available or is negative for HRR defects, the consensus on first-line mCRPC treatment was to recommend an ARPI if patients previously received ADT ± docetaxel, or docetaxel if they previously received ADT + ARPI. For patients whose tumours were negative for HRR defects and who had previously received ADT + ARPI + docetaxel, the consensus was to recommend ^{177}Lu-PSMA. Although consensus was not reached on how to manage patients without genomic testing, most panellists also recommended ^{177}Lu-PSMA for this scenario.

For patients in whom a pathogenic *BRCA2* alteration is identified, the consensus was to recommend an ARPI + PARPi combination if patients have previously received ADT (± docetaxel) for mHSPC, reflecting results from the PROpel, MAGNITUDE, and TALAPRO-2 trials [164–169]. However, consensus was not reached on how to treat patients who received ADT + ARPI or triplet therapy for mHSPC; for these scenarios, panellists were divided between switching to PARPi monotherapy, adding a PARPi to current therapy, or changing to an alternate ARPI plus a PARPi. Of note, all these options include use of a PARPi, indicating support for this therapeutic option. There is a need for studies evaluating these strategies (ie, switch to PARPi monotherapy, PARPi addition to current therapy, or changing ARPI and adding a PARPi) in patients with mCRPC who were previously treated with ADT + ARPI ± docetaxel.

For patients with tumours bearing alterations in HRR genes other than *BRCA2*, there was consensus in favour of recommending PARPi therapy for the same indication (ie, stage of disease) as for *BRCA2* alterations for patients with *BRCA1* alterations. Although there was no consensus on the management of patients with other non-*BRCA2* HRR gene alterations, 78% of panellists voted to recommend PARPi use in any disease setting for patients with *PALB2* alterations. Interestingly, this is in line with pooled analysis results recently published by the FDA, except that only 65% of panellists voted to recommend PARPi therapy for patients with inactivating *CDK12* alterations [176]. These voting results should be interpreted with caution, since even experts in the management of advanced PC may find it difficult to interpret some of these genomic alterations; not only is the topic very complex, but some pieces of information that may be crucial (eg, biallelic loss, or if the alteration is subclonal) is also not easily extracted or may not be available at all.

Although consensus on timing was not reached, almost all panellists (97%) recommended use of platinum-based therapy at some point in the mCRPC disease course (either before or after taxane chemotherapy) in patients with *BRCA2* alterations if PARPi could not be used. Because we asked about the timing of platinum use in terms of before or after a taxane, we did not provide the option to use a platinum-taxane combination as a first-line option, and this may have affected the voting results.

There has been much discussion on a direct switch from one ARPI to another in the treatment sequence, specifically for use as a control arm in clinical trials. Very few panellists recommended this switch for the majority of patients, instead supporting the opinion that an ARPI switch in a trial control arm is not adequate for unselected patients.

With regard to MDT, interestingly, only 14% of panellists supported its use alone (without a change of systemic therapy) in patients with oligometastatic mCRPC, whereas for oligoprogressive mCRPC, 49% of panellists supported the use of MDT to all progressing lesions without a change in systemic therapy.

Symptomatic fractures and SCC are highly morbid complications of advanced PC that can have a major impact on quality of life. Although no consensus was reached, most panellists (83%) recommended prophylactic RT for selected patients with progressing high-risk bone lesions or, in cases with disease progression in the spine, for patients with an epidural soft-tissue component (98%). This is despite the absence of benefit with these approaches in comparison to close monitoring in a recent randomised trial, perhaps because of certain weaknesses in the study design and the low event rate [198].

3.5. *^{177}Lu-PSMA therapy*

3.5.1. *Sequencing of ^{177}Lu-PSMA therapy*

At APCCC 2021 there was consensus on treatment with ^{177}Lu-PSMA for patients with mCRPC progressing after at least one line of ARPI and one line of chemotherapy [5].

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Since then, results from the PSMAfore trial (NCT04689828), which have been presented but not yet published, showed a significant rPFS benefit from ^{177}Lu-PSMA-617 in comparison to an ARPI switch in patients with taxane-naive mCRPC who had PSMA-positive PET findings [172]. Patients enrolled in the PSMAfore trial had to be candidates for an ARPI switch and unsuitable for or considered appropriate for deferral of docetaxel as judged by the treating physician. However, ^{177}Lu-PSMA-617 showed no OS benefit in the third interim analysis in either the intention-to-treat or crossover-adjusted analysis; 77.5% of patients who were randomised to the control arm had crossed over to ^{177}Lu-PSMA-617 therapy [172]. A press release for SPLASH (NCT04647526), which is evaluating ^{177}Lu-PSMA-PNT2002 (^{177}Lu-PSMA-I&T) in chemotherapy-naïve patients with mCRPC, reported a statistically significant improvement in rPFS. The trial results will be presented at ESMO 2024 [202]. At the time of APCCC 2024, ^{177}Lu-PSMA had no regulatory approval in the prechemotherapy space.

An important definition used at APCCC 2024 should be mentioned here: the term "PSMA PET" includes PSMA PET/CT and the rare cases in which PSMA PET/MRI is used. In addition, unless otherwise specified, PSMA PET refers to PSMA tracers for which reasonable data are available.

Panellists voted on two questions concerning second-line therapy in patients with mCRPC progressing on or after one line of ARPI, one in which patients were asymptomatic and the other in which they were symptomatic.

Q137: For the majority of chemotherapy fit asymptomatic patients with PSMA imaging-positive mCRPC who meet PET criteria for ^{177}Lu-PSMA therapy and have received one line of ARPI and no chemotherapy, what is your preferred treatment option assuming treatments are readily available and there is no actionable molecular alteration?

- Alternate ARPI: 1% (1 vote)
- ARPI + PARPi: 1% (1 vote)
- Docetaxel: 70% (66 votes)
- ^{177}Lu-PSMA: 28% (27 votes)
- Abstain/unqualified to answer (11 votes)

No consensus.

Q138: For the majority of chemotherapy fit symptomatic patients with PSMA imaging-positive mCRPC who meet relevant PET criteria for ^{177}Lu-PSMA therapy, who have received one line of ARPI and no chemotherapy, what is your preferred treatment option assuming treatments are readily available and there is no actionable molecular alteration?

- Alternate ARPI: 1% (1 vote)
- ARPI + PARPi: 0% (0 votes)
- Docetaxel: 82% (79 votes)
- ^{177}Lu-PSMA: 17% (16 votes)
- Radium-223: 0% (0 votes)
- Abstain/unqualified to answer (10 votes)

Consensus in favour of recommending docetaxel treatment for symptomatic patients with mCRPC and no actionable molecular alteration who have received one line of ARPI therapy.

Similar to APCCC 2021, the panel voted on their preferred next treatment option for patients with PSMA imaging–positive mCRPC meeting the relevant PET criteria for ^{177}Lu-PSMA therapy and receipt of one line of ARPI treatment and one line of taxane-based chemotherapy [5]. To date, two trials have evaluated the role of ^{177}Lu-PSMA therapy in mCRPC after ARPI and after taxane chemotherapy [203–205].

Q139: For the majority of chemotherapy fit patients with PSMA imaging-positive mCRPC who meet relevant PET criteria for ^{177}Lu-PSMA therapy, who have received one line of ARPI and one line of taxane-based chemotherapy, what is your preferred treatment option assuming treatments are readily available and there is no actionable molecular alteration?

- Alternate ARPI: 0% (0 votes)
- ^{177}Lu-PSMA: 96% (90 votes)
- Cabazitaxel: 4% (4 votes)
- Radium-223: 0% (0 votes)
- Abstain/unqualified to answer (12 votes)

Strong consensus in favour of recommending treatment with ^{177}Lu-PSMA for patients with mCRPC and no actionable molecular alteration who have received docetaxel and an ARPI.

3.5.2. Patient selection for RLT and monitoring

Randomised prospective trials on RLT in this setting (phase 2: TheraP; phase 3 PSMAfore and VISION) applied different approaches for patient selection [172,203–205]. In TheraP, all patients were screened with both PSMA PET/CT and fluorodeoxyglucose (FDG) PET/CT [203,204]. In the PSMAfore and VISION trials, baseline imaging consisted of PSMA PET accompanied by contrast-enhanced CT [172,205]. Of note, TheraP excluded approximately 28% of patients on the basis of imaging, while PSMAfore excluded 9% and VISION excluded ~13% [172,203–205]. In TheraP, patients who were excluded had an OS of 11.0 mo, compared to 18.8 mo among patients randomised to either ^{177}Lu-PSMA-617 or cabazitaxel (HR 0.42; $p < 0.001$) [204]. In TheraP, the PSMA mean standardised uptake value on PET was predictive of a higher likelihood of response to ^{177}Lu-PSMA in comparison to cabazitaxel, while the metabolic tumour volume on FDG PET was prognostic [206].

The panel voted on their preferred imaging for selection of patients for ^{177}Lu-PSMA therapy, assuming that all imaging modalities are available.

Q140: In the majority of patients that you evaluate for ^{177}Lu-PSMA therapy eligibility, what imaging do you routinely recommend assuming all scans are readily available?

- PSMA PET plus FDG PET (like in the TheraP study): 24% (23 votes)
- PSMA PET and bone scintigraphy (like in the VISION study): 33% (31 votes)
- PSMA PET and add FDG PET selectively for equivocal cases: 43% (40 votes)

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- No PSMA PET imaging needed: 0% (0 votes)
- Abstain/unqualified to answer (12 votes)

No consensus.

A combined total of 100% voted in favour of PSMA PET imaging for evaluation of ^{177}Lu-PSMA eligibility.

Monitoring of patients on ^{177}Lu-PSMA therapy was discussed both as a general question and specifically in terms of which imaging modalities to use. Patients in clinical trials are generally closely monitored according to the Prostate Cancer Working Group 3 (PCWG3) recommendations. In the VISION trial, conventional imaging (CT and bone scintigraphy) was performed every 8 wk for 24 wk, and then every 12 wk; in TheraP, conventional imaging was performed every 12 wk [203–205,207]. ^{177}Lu-PSMA therapy allows subsequent quantitative ^{177}Lu single-photon emission CT (SPECT)/CT imaging for longitudinal evaluation of the presence of the PSMA target and monitoring of the treatment response [208–210].

Q141: In the majority of patients on treatment with ^{177}Lu-PSMA, do you recommend imaging for response monitoring during ^{177}Lu-PSMA treatment in the absence of clinical progression?

- Yes, in the majority of patients: 70% (67 votes)
- Yes, but only in selected patients: 22% (21 votes)
- No: 8% (8 votes)
- Abstain/unqualified to answer (10 votes)

No consensus

A combined total of 92% voted in favour of recommending imaging for response monitoring, at least in selected patients.

Q142: In the majority of patients on treatment with ^{177}Lu-PSMA, which imaging modality do you recommend for response monitoring?

- Conventional imaging: 20% (19 votes)
- PSMA PET (no iodine iv contrast): 25% (23 votes)
- PSMA PET plus diagnostic CT (with iv iodine contrast): 41% (38 votes)
- LuPSMA SPECT/CT: 14% (13 votes)
- Abstain/unqualified to answer (13 votes)

No consensus.

In the VISION trial, patients who showed a radiologic, PSA, and/or clinical response to four cycles of ^{177}Lu-PSMA-617 could receive two more cycles of treatment if they had tolerated therapy well and showed evidence of residual disease on contrast-enhanced CT, MRI, or bone scintigraphy [205]. In TheraP, patients could receive a total of up to six cycles of ^{177}Lu-PSMA-617 therapy, starting with a higher dose that was reduced at each cycle; treatment was paused earlier in 7% of individuals with exceptional responses according to SPECT/CT imaging [203,204]. The PSMAfore trial used six cycles of treatment [172]. The SPLASH trial used a different dose (6.8 GBq per cycle) and patients were treated every 8 wk for four cycles [202].

The panel voted on two clinical scenarios regarding the number of treatment cycles to recommend for patients responding to ^{177}Lu-PSMA: one in which PSMA imaging shows no remaining uptake after four cycles, and one in which there is significant remaining uptake.

Q143: In the majority of patients with response (PSA and/or clinical and/or radiological) to ^{177}Lu-PSMA therapy after 4 cycles, do you recommend completion of the 6 cycles if PSMA-based imaging shows significant remaining uptake (as defined by the treating physician)?

- Yes, in the majority of patients: 76% (71 votes)
- Yes, but only in selected patients:18% (17 votes)
- No: 6% (5 votes)
- Abstain/unqualified to answer (13 votes)

Consensus in favour of completion of six cycles in the majority of patients if PSMA-based imaging shows significant remaining uptake.

Q144: In the majority of patients with response (PSA and/or clinical and/or radiological) to ^{177}Lu-PSMA therapy after 4 cycles, do you recommend completion of the 6 cycles if PSMA-based imaging shows no remaining uptake (as defined by the treating physician)?

- Yes, in the majority of patients: 18% (17 votes)
- Yes, but only in selected patients: 25% (23 votes)
- No: 57% (52 votes)
- Abstain/unqualified to answer (14 votes)

No consensus.

All patients in the VISION trial received protocol-permitted SOC therapy, most commonly with corticosteroids (64%) and/or ARPIs (57%) [205]. ARPIs exhibit only minimal to moderate antitumour activity if given sequentially, and guidelines recommend that this sequence should be avoided because of known cross-resistance and the availability of other treatments [73,188,211]. However, ARPIs may upregulate PSMA expression, thereby increasing the efficacy of ^{177}Lu-PSMA, raising the question of whether a Lu-PSMA + ARPI combination is clinically advisable [212–215]. In the PSMAfore and TheraP trials, combination with ARPI was not allowed [172,203,204]. The VISION trial allowed an ARPI as SOC therapy in conjunction with ^{177}Lu-PSMA-617, and 52% of the patients received this combination in the experimental arm [205].

The randomised ENZA-p trial (NCT04419402) compared ^{177}Lu-PSMA-617 + enzalutamide to enzalutamide alone in patients with first-line mCRPC at high risk of early progression on enzalutamide (prior abiraterone and/or docetaxel for hormone-sensitive disease were allowed) [216]. ^{177}Lu-PSMA-617 was administered at a dose of 7.5 GBq on days 15 and 57, with two further doses if persistent PSMA-positive disease was detected on interim ^{68}Ga-PSMA PET (day 92). Patients who received the combination showed better PSA-PFS and PSA response rates in comparison to patients who received enzalutamide alone [216]. As with many combination trials, this trial does not answer the question of whether antitumour activity of the combination is higher than when giving the two treatments in sequence. At least theoretically, however, the close intracellular rela-

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tionship and interaction of androgen receptors and PSMA receptors may facilitate a synergistic effect.

The APCCC 2024 panel considered whether patients should receive ^{177}Lu-PSMA as monotherapy or in combination with an ARPI if they have or have not been exposed to a taxane.

Q145: For the majority of patients treated with ^{177}Lu-PSMA in the mCRPC setting post ARPI and post-chemotherapy, do you recommend the combination with the alternate ARPI?

- Yes, in the majority of patients: 9% (9 votes)
- Yes, but only in selected patients: 18% (17 votes)
- No: 73% (69 votes)
- Abstain/unqualified to answer (11 votes)

No consensus.

Q146: For the majority of patients treated with ^{177}Lu-PSMA in the mCRPC setting post ARPI and no prior chemotherapy, do you recommend the combination with the alternate ARPI?

- Yes, in the majority of patients: 10% (10 votes)
- Yes, but only in selected patients: 19% (18 votes)
- No: 71% (67 votes)
- Abstain/unqualified to answer (11 votes)

No consensus.

The APCCC 2024 panel also voted on a question regarding whether or not it is appropriate to extrapolate data generated for ^{177}Lu-PSMA-617 to treatment using alternative PSMA ligands. This question is relevant because the availability of ^{177}Lu-PSMA-617 is limited in many places for both logistic and financial reasons. A meta-analysis of published data showed similar PSA response rates and pharmacokinetic parameters for ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T [217]. ^{177}Lu-PSMA-I&T has had extensive off-trial use globally, with first use predating the introduction of ^{177}Lu-PSMA-617. A recent survey of 95 theranostic centres showed that 22% of centres use ^{177}Lu-PSMA-I&T only and 27% use ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-617 [218]. Details of the SPLASH trial evaluating ^{177}Lu-PSMA-I&T in PSMA-positive mCRPC following progression on an ARPI will be presented at ESMO 2024.

Q147: Can the data generated by PSMAfore and VISION with lutetium-PSMA-617 be extrapolated to lutetium-PSMA with alternate PSMA ligands?

- Yes, for all PSMA ligands: 25% (20 votes)
- Yes, but only for PSMA-I&T: 19% (15 votes)
- No: 56% (45 votes)
- Abstain/unqualified to answer (26 votes)

No consensus.

Only limited data on ^{177}Lu-PSMA rechallenge are available. The evidence available suggests that retreatment is feasible, albeit with a lower probability of response and durability of response [219–221]. The panel voted on one question regarding rechallenge in patients who have received six cycles of ^{177}Lu-PSMA.

Q148: Do you recommend re-treatment with lutetium-PSMA (if relevant PET criteria are met) in the disease course in patients who have previously responded to 6 cycles of ^{177}Lu-PSMA treatment?

- Yes: 12% (11 votes)
- Yes, but only if response of >6 months: 59% (52 votes)
- No: 29% (26 votes)
- Abstain/unqualified to answer (17 votes)

No consensus.

Ineligibility criteria for the PSMAfore and VISION trials included adequate bone marrow function, defined as an absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, and haemoglobin ≥ 90 g/l [203–205]. Limited data are available on ^{177}Lu-PSMA therapy for patients with impaired bone-marrow function, although it has been reported that high tumour burden in bone, grade 2 baseline cytopenia, and previous taxane-based chemotherapy are associated with a higher risk of haematological toxicity [222]. A retrospective multicentre series found that among heavily pretreated patients with diffuse marrow involvement, ^{177}Lu-PSMA demonstrated relevant antitumour activity and acceptable toxicity [223].

The panel voted on two questions regarding their preferred treatment for patients with impaired bone-marrow function, one on chemotherapy-naïve patients and the other on patients progressing on or after an ARPI and docetaxel:

Q149: In the majority of patients with mCRPC (no DDR alteration) progressing on or after an ARPI and relevant impaired bone marrow function (haemoglobin <90 g/l and/or neutrophils $<1.5 \times 10^9$/l and/or platelets $<100 \times 10^9$/l), what do you recommend?

- Docetaxel 3-weekly: 12% (10 votes)
- Docetaxel weekly or 2-weekly: 49% (40 votes)
- ^{177}Lu-PSMA: 6% (5 votes)
- ^{177}Lu-PSMA reduced administered activity: 12% (10 votes)
- Alternate ARPI: 12% (10 votes)
- Radium-223: 0% (0 votes)
- Best supportive care: 9% (7 votes)
- Abstain/unqualified to answer (24 votes)

No consensus.

Q150: In the majority of patients with mCRPC (no DDR alteration) progressing on or after an ARPI and docetaxel and relevant impaired bone marrow function (haemoglobin <90 g/l and/or neutrophils <1.5 x 10^9/l and/or platelets <100 x 10^9/l), what do you recommend?

- Cabazitaxel 3-weekly: 8% (7 votes)
- Cabazitaxel weekly or 2-weekly: 24% (20 votes)
- ^{177}Lu-PSMA: 12% (10 votes)
- ^{177}Lu-PSMA reduced administered activity: 27% (22 votes)
- Alternate ARPI: 17% (14 votes)
- Radium-223: 0% (0 votes)
- Best supportive care: 12% (10 votes)

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- Abstain/unqualified to answer (23 votes)

No consensus.

The PSMAfore trial required good renal function with an estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73 m^2 according to the Modification of Diet in Renal Disease equation [172]. The VISION trial applied similar inclusion criteria for renal function (serum/plasma creatinine ≤1.5 times the upper limit of normal or creatinine clearance ≥50 ml/min) [203,204]. In VISION, the incidence of acute renal injury was low, with grade ≥3 events observed in 4.3% of patients. In a retrospective analysis of data for 46 patients treated with ^{177}Lu-PSMA, pretreatment eGFR was an independent predictor of renal toxicity [224].

A retrospective analysis of data for 106 patients receiving a minimum of four doses of ^{177}Lu-PSMA-I&T showed a 20% decrease in GFR after 24 mo and identified several risk factors, namely hypertension, diabetes, age >65 yr, and prior taxane chemotherapy [225]. In another series of 22 patients with mCRPC and impaired renal function (GFR ≤60 ml/min) who received ^{177}Lu-PSMA-617, only one patient experienced deterioration of renal function; GFR in other patients remained stable or even improved, possibly because of improvement in PC-related ureteric obstruction with treatment [226]. The FDA does not recommend ^{177}Lu-PSMA-617 for patients with GFR <30 ml/min.

The panel voted on two questions concerning their preferred treatment for patients with impaired renal function, one for chemotherapy-naïve patients and the other for patients progressing on or after an ARPI and docetaxel.

Q151: In the majority of patients with mCRPC (no DDR alteration) progressing on or after an ARPI and impaired renal function (GFR 30–49 ml/min), what do you recommend?

- Docetaxel: 73% (65 votes)
- ^{177}Lu-PSMA: 7% (6 votes)
- ^{177}Lu-PSMA reduced administered activity: 11% (10 votes)
- Alternate ARPI: 7% (6 votes)
- Radium-223: 2% (2 votes)
- Abstain/unqualified to answer (17 votes)

No consensus.

Q152: In the majority of patients with mCRPC (no DDR alteration) progressing on or after an ARPI and docetaxel and impaired renal function (GFR 30–49 ml/min), what do you recommend?

- Cabazitaxel: 42% (36 votes)
- ^{177}Lu-PSMA: 21% (18 votes)
- ^{177}Lu-PSMA reduced administered activity: 25% (22 votes)
- Alternate ARPI: 7% (6 votes)
- Radium-223: 5% (4 votes)
- Abstain/unqualified to answer (20 votes)

No consensus.

Prospective randomised clinical trials are evaluating ^{177}Lu-PSMA in mHSPC. Relevant studies include UpFrontPSMA (NCT04343885) and PSMAaddition (NCT04720157) [227]. To date, study findings have not been reported. The panel voted on a question on whether or not it is appropriate to use ^{177}Lu-PSMA in mHSPC.

Q153: Is it appropriate to recommend lutetium-PSMA therapy in patients with mHSPC outside of a clinical trial?

- Yes: 7% (7 votes)
- No: 93% (93 votes)
- Abstain/unqualified to answer (6 votes)

Strong consensus against recommending ^{177}Lu-PSMA therapy for patients with mHSPC outside a clinical trial.

3.5.3. *Discussion on ^{177}Lu-PSMA therapy*

Supplementary Figure 5 provides graphical representations of the voting results for questions on ^{177}Lu-PSMA therapy.

As in 2022, APCCC 2024 panellists again reached consensus that they prefer ^{177}Lu-PSMA therapy for patients with mCRPC previously treated with an ARPI and a taxane; this consensus is in keeping with results from the VISION trial [5]. This changed when panellists were asked to assume that patients had impaired renal or bone-marrow function: in these situations, substantially fewer panellists (46% and 39%, respectively) would recommend ^{177}Lu-PSMA treatment, even at a reduced dose. As in registrational trials of other treatments, patients with impaired renal or bone-marrow function were excluded from ^{177}Lu-PSMA trials, and safety data for these patients are currently only available from small retrospective studies. Now that ^{177}Lu-PSMA is registered/approved and available, experience and evidence on these more challenging scenarios will evolve rapidly.

Interestingly, only a minority of panel members recommended ^{177}Lu-PSMA as standard treatment for patients with no prior chemotherapy exposure and whose PC is progressing on or after ARPI therapy. This is probably related to the fact that at the time of APCCC 2024, the PSMAfore trial results had not been published; subsequent data reported for this trial did not demonstrate a significant OS benefit from ^{177}Lu-PSMA-617 in comparison to an ARPI switch [172]. An updated OS analysis presented at ASCO 2024 showed an unadjusted HR of 0.98 (95% CI 0.75–1.28) and a high crossover rate of 57.3% among patients in the ARPI group [228]. At APCCC 2024, there was consensus to instead recommend docetaxel for chemotherapy-fit patients with mCRPC who are symptomatic and progressing on or after an ARPI. However, many patients are medically unsuitable for taxane therapy owing to age and comorbidities; for these patients, ^{177}Lu-PSMA is a treatment option on the basis of data from the PSMAfore trial.

Consensus was also not reached on the optimal imaging modalities for determining suitability for ^{177}Lu-PSMA treatment; however, 100% of panellists agreed that a PSMA PET/CT scan with or without some other imaging modality should be performed. This implies that the panel believes that ^{177}Lu-PSMA should not be offered without some type of PSMA-based imaging selection, although this question was not specifically asked.

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Panellists did not reach consensus on how to monitor ^{177}Lu-PSMA responses, although only 8% voted against the use of imaging for this purpose. The question of monitoring remains open, possibly because of regional disparities in nuclear medicine practices and imaging reimbursement standards. Published work has demonstrated the value of interim PSMA PET/CT and PSMA SPECT/CT in monitoring and assessing responses to ^{177}Lu-PSMA therapy [208,229]. However, there is a need for criteria to define PSMA PET/CT or post-therapy SPECT/CT progression that warrants treatment cessation; such criteria would help clinicians in standardising practice and assessing outcomes. Unlike PET/CT, SPECT/CT involves dosimetry, which may represent an additional biomarker [230]. Of note, a patient experience substudy of TheraP showed that from a psychological perspective, patients found SPECT/CT useful for an understanding of their treatment response [231].

According to voting results, panel members were confident that ^{177}Lu-PSMA can be interrupted after four cycles if imaging shows no remaining uptake, but that treatment should continue for a total of six cycles if relevant tumour activity is detected on PSMA-based imaging. The doses administered and scheduling of ^{177}Lu-PSMA vary among studies, and the optimal approach is yet to be defined. The same is true for rechallenge; a majority of panellists (but not a consensus) voted to recommend rechallenge, but only if the response to the first round of therapy lasts for >6 mo. The 6-mo time frame was chosen as an answer option because it is often used in oncology when patients receive chemotherapy on rechallenge, particularly when platinum-based therapy is considered. Data on rechallenge in patients receiving ^{177}Lu-PSMA treatment are limited, but this approach appears to be efficacious in a subgroup of patients who respond to the first round of treatment. Questions requiring further study included when ^{177}Lu-PSMA treatment should be paused and restarted, at what time intervals, and on the basis of what biomarkers.

A majority of the panel (>70%, but not a consensus) voted against combining ^{177}Lu-PSMA with an ARPI for the majority of both PSMAfore-like and VISION-like patients. PSMAfore and TheraP did not add an ARPI to^{177}Lu-PSMA-617, while 52% of patients receiving ^{177}Lu-PSMA-617 in VISION were also receiving a second- or third-line ARPI [172,203–205]. While ENZA-p provided evidence that ^{177}Lu-PSMA-617 addition to first-line enzalutamide was effective in prolonging the depth and duration of responses in patients with mCRPC, it did not answer the question of whether addition of a second-line ARPI to ^{177}Lu-PSMA-617 is beneficial [216]. The data available to date are encouraging, but further research is required to determine the value of adding second-line ARPI therapy to standard ^{177}Lu-PMSA-617 in patients with mCRPC either before or after chemotherapy.

There was strong consensus against recommending treatment with ^{177}Lu-PSMA in the mHSPC setting until clinical trial data are mature. Phase 2 trials of other combinations, such as radium-223, cabazitaxel, PARPi, and immunotherapy, are also being reported and will inform clinical decision-making directions in the future [232,233].

Only a minority of panellists voted in favour of ^{177}Lu-PSMA treatment for patients with mCRPC who have received an ARPI and have impaired bone-marrow or renal function, with the majority voting instead for docetaxel. For patients who have already received both an ARPI and taxane-based chemotherapy and have relevant bone-marrow or renal function impairment, more panel members voted for ^{177}Lu-PSMA either at the full dose or a reduced dose. These questions were prompted by the realisation that many patients encountered in routine practice would not meet the eligibility criteria for the registrational ^{177}Lu-PSMA trials. However, most APCCC 2024 panellists acknowledged that clinical data for many of these scenarios are limited, and consensus was not reached for any of these questions. Hence, it is crucial to contextualise these voting outcomes within clinical scenarios and to consider all available evidence-supported treatment options and patients' potential eligibility for clinical trials.

These results offer a practical framework to aid clinicians in discussions with patients and to foster shared and multidisciplinary decision-making, ideally with the involvement of nuclear medicine specialists in multidisciplinary team meetings [234].

3.6. *Side effects of systemic therapy and ARPI selection in special situations*

3.6.1. *Cardiovascular risk assessment and monitoring*

Cardiovascular events are a significant cause of morbidity and mortality among patients with advanced PC [235]. Numerous factors, including age, male phenotype, obesity, familial cardiovascular disease, tobacco use, diabetes, and sedentary lifestyle, among others, contribute to greater susceptibility to cardiovascular events in this population [236–240]. In addition, ADT is associated with increases in low-density lipoprotein cholesterol and triglyceride levels and visceral fat, a decrease in lean body mass, an increase in insulin resistance, and a decrease in glucose tolerance [241,242]. These changes can predispose patients to metabolic syndrome and accelerate atherosclerosis, resulting in higher risk of coronary artery disease [243–247]. ADT is associated with both arterial and venous thromboembolic events, and can ultimately increase rates of acute myocardial infarction and heart failure, and cardiovascular morbidity and mortality rates overall [241,244,248–250]. ADT is also associated with QT-interval prolongation and therefore with a theoretical increase in the risk of arrhythmia and sudden cardiac death [241,244,249–251]. Use of AR antagonists has been associated with QTc prolongation [252]. Pre-existing long-QT syndrome can easily be detected via an electrocardiogram (ECG).

An important area of debate concerns differences in cardiotoxicity between luteinising hormone–releasing hormone (LHRH) agonists and antagonists [253–255]. A prespecified safety analysis of the HERO trial, which compared the LHRH antagonist relugolix to the LHRH agonist leuprorelin, revealed a higher risk of major adverse cardiovascular events (MACE) with LHRH agonists, particularly among patients with a history of MACE [254]. The higher risk of cardiac events with LHRH agonists may be because LHRH agonists, but not antagonists, may induce atherosclerotic plaque instability and rupture, which is possibly related to compensatory rises in follicle-stimulating hor-

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mone observed with LHRH agonists. PRONOUNCE, a randomised phase 3 trial designed to prospectively compare the cardiovascular safety of LHRH antagonist versus agonist therapy in patients with PC and pre-existing atherosclerotic disease, was terminated prematurely because of low accrual [255]. No differences in MACE at 1 yr were found between the degarelix and leuprolide arms [255]. However, as the trial enrolled only 61% of the planned 900 patients and the MACE incidence was lower than estimated, confidence intervals were wide and the statistical power was low; consequently, the relative cardiovascular safety of LHRH antagonists and agonists remains unclear. Reassuringly, data from this trial suggest that the close medical monitoring and care performed as part of the study protocol may have contributed to the low MACE rate.

Addition of a potent ARPI such as abiraterone, apalutamide, darolutamide, or enzalutamide to ADT has been linked to an increase in cardiovascular events in several clinical trials and in large cohort studies [252,256–258]. A meta-analysis of data from 24 randomised clinical trials revealed that ARPI addition to ADT was associated with a twofold increase in cardiovascular morbidity in comparison to ADT alone [259]. However, when normalised for time on study, the difference was far less prominent.

The increase in cardiovascular risk observed with abiraterone results from its mechanism of action: CYP17 inhibition and reduced testosterone levels lead to a decrease in glucocorticoid production and a compensatory increase in adrenocorticotrophic hormone, resulting in a rise in steroids with mineralocorticoid properties upstream of CYP17A1, which can lead to a syndrome of secondary mineralocorticoid excess characterised by water retention, hypertension, and possible heart failure [260]. Concomitant use of prednisone reduces the compensatory feedback increase in mineralocorticoids and is the reason why abiraterone is used in combination with prednisone. Addition of an ARPI to ADT may also increase levels of triglycerides and cholesterol further than with ADT alone [125].

Discussions at APCCC 2024 focused on the necessity of conducting cardiovascular assessments before initiating systemic therapy and the importance of monitoring patients receiving ARPIs.

Q154: Do you recommend a cardiovascular risk assessment (eg, ESC, ASCVD, U-prevent…) in patients with advanced prostate cancer starting systemic therapy (ADT ± ARPI)?

- Yes, in the majority of patients: 33% (35 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 56% (59 votes)
- No, standard clinical assessment: 11% (11 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

A combined total of 89% voted in favour of recommending a cardiovascular risk assessment, at least in selected patients with a history of MACE or other risk factors for cardiac disease.

Q155: Do you recommend a baseline ECG before starting systemic hormonal therapy (ADT ± ARPI)?

- Yes, in the majority of patients: 33% (34 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 48% (50 votes)
- No: 19% (20 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 81% voted in favour of recommending a baseline ECG before starting systemic hormonal therapy, at least in selected patients with a history of a MACE or other risk factors for cardiac disease.

Q156: Do you recommend a cardiac evaluation (for example stress test and/or echocardiography in addition to ECG) before starting ADT?

- Yes, in the majority of patients: 7% (8 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 67% (70 votes)
- No: 26% (27 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

Q157: Do you recommend a cardiac evaluation (for example echocardiography and/or stress test in addition to ECG) before starting abiraterone in addition to ADT?

- Yes, in the majority of patients: 20% (20 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 56% (58 votes)
- No: 24% (25 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

A combined total of 76% voted in favour of recommending a cardiac evaluation before starting abiraterone in addition to ADT, at least in selected patients with a history of a MACE or other risk factors for cardiac disease.

Q158: Do you recommend a cardiac evaluation (echocardiography and/or stress test in addition to ECG) before starting an AR antagonist (Apa, Daro, Enza) in addition to ADT?

- Yes, in the majority of patients: 15% (15 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 56% (58 votes)
- No: 29% (30 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

Q159: For the majority of patients starting systemic hormonal therapy (ADT ± ARPI), do you recommend monitoring lipid-profiles?

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- Yes baseline: 13% (13 votes)
- Yes, baseline and regularly, eg, every 6–12 months: 70% (73 votes)
- No: 17% (18 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 83% voted in favour of recommending monitoring of lipid profiles, at least at baseline.

Q160: Do you recommend blood pressure monitoring in patients on abiraterone therapy?

- Yes, in the majority of patients: 95% (100 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 4% (4 votes)
- No: 1% (1 vote)
- Abstain/unqualified to answer (1 vote)

Strong consensus in favour of blood pressure monitoring in patients on abiraterone therapy.

Q161: Do you recommend blood pressure monitoring in patients on AR antagonist (Apa, Daro, Enza) therapy?

- Yes, in the majority of patients: 75% (78 votes)
- Yes, but only in selected patients with a history of a major adverse cardiac event (MACE) or other risk factors for cardiac disease: 17% (18 votes)
- No: 8% (8 votes)
- Abstain/unqualified to answer (2 votes)

Consensus in favour of blood pressure monitoring in patients on AR antagonist therapy.

Q162: For the majority of patients with advanced prostate cancer with a recent history of major adverse cardiac event (MACE) with an indication for ADT, what is your preferred GnRH analogue?

- LHRH agonist: 5% (5 votes)
- LHRH antagonist: 71% (73 votes)
- Orchiectomy: 3% (3 votes)
- Either one of the options above: 21% (22 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

3.6.2. *Hot flushes*

Hot flushes, a prevalent side effect of hormonal therapies used to treat PC, affect 40–80% of patients within 3 mo of treatment initiation and can cause significant distress, sleep disturbances, and diminished quality of life [261–265]. Hot flushes may reduce ADT compliance and are a major contributor to discontinuation of therapy [250]; they appear to be a manifestation of the lack of oestrogen in the ADT setting. The specific mechanism is disruption of the equilibrium of neurotransmitters, in particular oestrogen and neurokinin B acting on the kisspeptin, neurokinin B, and dynorphin neurons that project to the median preoptic nucleus to cause vasomotor symptoms [266]. A small study of 60 patients receiving ADT for PC found that hot flushes were more pronounced among younger patients, patients with lower body mass index, and patients with certain genetic polymorphisms associated with vasoconstriction, immune function, neurotransmission, and circadian rhythms [267].

Not surprisingly, iADT led to a reduction in hot flushes in comparison to cADT [268]; conversely, addition of an ARPI to ADT appeared to result in an increase in the incidence of hot flushes in comparison to ADT alone [269].

Lifestyle management principles for reducing the frequency and severity of hot flushes include avoiding various triggers such as hot beverages, alcohol, hot or spicy food, radiant heaters, and thermal blankets [267,270]. In addition, patients can be encouraged to dress in layers, undertake both resistance and aerobic exercise, and maintain a cool home environment to mitigate hot flushes [271]. Other non-pharmaceutical measures, such as cognitive behavioural therapy (CBT), have been investigated with some success in nonrandomised trials. Results from MANCAN2, a randomised trial evaluating the value of virtual self-help CBT, were presented after APCCC 2024 at ASCO 2024 [272]. In this study of patients with PC who were receiving ADT, CBT addition to usual treatment improved the severity of hot flushes and night sweats in the short term, but the benefits were not maintained at 6 mo [272]. The role of acupuncture has also been investigated and led to an 89–95% decrease in symptoms, although these results are not from a randomised trial [273].

Pharmaceutical management of hot flushes can be classified into oestrogenic and non-oestrogenic approaches. Concerns about the cardiovascular risks of oestrogens such as diethylstilboestrol have been raised [274,275]. The PATCH trial is evaluating the safety and efficacy of transdermal oestradiol (tE2) patches as a substitute for conventional ADT. According to recently published preliminary results, patients in the tE2 arm were less likely to experience hot flushes (8% vs 46%) and reported better quality of life than patients on LHRH analogues; patients in the two arms had very similar castration rates up to 12 mo after starting therapy [276]. However, the rate of gynaecomastia was significantly higher in the tE2 group (37% vs 5% in the conventional-ADT arm) [277]. Use of lower-dose transdermal oestrogen (to avoid the risk of thrombosis) has also been effective, but was accompanied by troublesome rates of gynaecomastia and nipple tenderness in comparison to ADT alone (44% vs 21%, and 28% vs 3%, respectively). The PATCH trial showed no difference in cardiovascular events with cutaneous administration of oestrogens [277].

Non-oestrogenic approaches for management of hot flushes include drugs such as venlafaxine, gabapentin, medroxyprogesterone, and cyproterone acetate. Decreases in PSA levels after discontinuing cyproterone acetate or medroxyprogesterone suggest that these drugs may possibly contribute to PC progression because of potential cross-activation of a mutated AR [275,278]. At ASCO 2024, investigators reported on a double-blind, placebo-controlled phase 2 trial (n = 88) in which either low or higher doses of the anticholinergic drug oxybutynin significantly reduced the frequency of hot flushes in comparison to placebo [279]. The low-dose cohort received 2.5 mg of oxybutynin twice daily, while the higher-dose cohort

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received 5 mg of oxybutynin twice daily; dry mouth was the adverse event most frequently reported.

Fezolinetant, a neurokinin 3 receptor antagonist, was recently approved by the FDA for the treatment of hot flushes on the basis of results from a randomised phase 3 trial in postmenopausal patients [280]. No data for patients on ADT are currently available.

Q164: For the majority of patients, what do you recommend as non-drug management options for frequent or bothersome hot flushes in addition to lifestyle changes?

- Exercise: 43% (43 votes)
- Acupuncture: 6% (6 votes)
- Both of the above: 51% (50 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

A combined total of 94% voted in favour of exercise.

Q165: For the majority of patients, what is your preferred drug management option for frequent or bothersome hot flushes in addition to lifestyle changes?

- Gabapentin: 9% (8 votes)
- Venlafaxine: 43% (37 votes)
- Cyproterone acetate: 21% (18 votes)
- Megestrol acetate: 11% (9 votes)
- Oxybutynin: 9% (8 votes)
- Fezolinetant: 1% (1 vote)
- Low-dose oestrogens: 6% (5 votes)
- Abstain/unqualified to answer (20 votes)

No consensus.

3.6.3. ARPI selection in special situations

At APCCC 2017, panellists voted on their choice of ADT in countries that have limited health care resources. For patients with metastatic PC, 90% of panel members voted for orchiectomy as ADT, while the remaining 10% voted for LHRH agonist therapy [3]. When reporting on this result, the panel concluded that while orchiectomy may be recommended as the first choice for ADT in this scenario, sociocultural and psychological barriers to such an intervention must be incorporated into treatment decisions.

In 2024, the panel voted on one question regarding a switch from LHRH analogues to orchiectomy in patients on long-term ADT to conserve health care resources.

Q163: For patients with metastatic prostate cancer on permanent ADT, should healthcare systems recommend switching from LHRH agonist/antagonists to bilateral subcapsular orchiectomy to spare health care resources?

- Yes: 40% (41 votes)
- No: 60% (61 votes)
- Abstain/unqualified to answer (4 votes)

No consensus.

The APCCC 2024 panel voted on the preferred choice of ARPI for patients with relevant pre-existing comorbidities and for older patients. This is relevant because of strong evidence that some AR antagonists increase the risk of falls, neurocognitive impairment, fatigue, and fractures [281–283]. Darolutamide generally appears to be a better-tolerated option in this vulnerable population [116,284–287]. A recently published review highlighted that the benefit of ARPIs observed in landmark phase 3 clinical trials may be limited to younger patients with good performance status in the real world [288]. Ongoing large clinical trials (eg, PREPARE and PEACE6-Vulnerable) may eventually improve consensus by clarifying how older age and/or frailty affect outcomes and management considerations.

Another relevant topic is polypharmacy, which is common among patients with advanced PC [289,290]. Numerous drug-drug interactions (DDIs) have been identified, with a focus on enzalutamide and apalutamide, and, to a lesser extent, darolutamide [291,292]. Abiraterone has several known DDIs [292,293]. Notably, novel anticoagulants, statins, antihypertensives, and antibiotics are among the most relevant medications prone to DDIs in PC treatment. Therefore, when patients are prescribed these drugs, it is crucial to refer to prescribing information or use online DDI tools for guidance. There is a continued need for ongoing trials and education to optimise both cardio-oncological and neuro-oncological assessment and management.

Q166: For the majority of patients with advanced prostate cancer and a history of falls, what is your preferred ARPI (any treatment line, assuming all options are available)?

- Abiraterone: 32% (32 votes)
- Apalutamide: 4% (4 votes)
- Darolutamide: 59% (58 votes)
- Enzalutamide: 0% (0 votes)
- Any of the above: 5% (5 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

Q167. For the majority of patients with advanced prostate cancer and a history of coronary artery disease and currently on oral anticoagulants and a statin, what is your preferred ARPI (any treatment line, assuming all options are available)?

- Abiraterone: 11% (11 votes)
- Apalutamide: 3% (3 votes)
- Darolutamide: 66% (63 votes)
- Enzalutamide: 4% (4 votes)
- Any of the above: 16% (15 votes)
- Abstain/unqualified to answer (10 votes)

No consensus.

Q168: For the majority of patients with advanced prostate cancer and a history of cognitive impairment, what is your preferred ARPI (any treatment line, assuming all options are available)?

- Abiraterone: 29% (29 votes)
- Apalutamide: 7% (7 votes)
- Darolutamide: 57% (57 votes)
- Enzalutamide: 0% (0 votes)

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- Any of the above: 7% (7 votes)
- Abstain/unqualified to answer (6 votes)

No consensus.

Q169: For the majority of patients with advanced prostate cancer and a history of relevant fatigue, what is your preferred ARPI (any treatment line, assuming all options are available)?

- Abiraterone: 40% (40 votes)
- Apalutamide: 7% (7 votes)
- Darolutamide: 44% (44 votes)
- Enzalutamide: 0% (0 votes)
- Any of the above: 9% (9 votes)
- Abstain/unqualified to answer (6 votes)

No consensus.

Irrespective of clinical trial data and assuming that all options are available, the panel voted on their preferred ARPI for patients aged ≥75 yr with mHSPC or mCRPC, taking into account all the considerations discussed above.

Q170: For the majority of patients with mHSPC ≥75 years of age, what is your ARPI of choice in any line with regards to efficacy and the safety profile in this patient population assuming all options are available?

- Abiraterone: 11% (11 votes)
- Apalutamide: 7% (7 votes)
- Darolutamide: 62% (61 votes)
- Enzalutamide: 1% (1 vote)
- Any of the above: 19% (18 votes)
- Abstain/unqualified to answer (8 votes)

No consensus.

Q171: For the majority of patients with mCRPC ≥75 years of age, what is your ARPI of choice in any line with regards to efficacy and the safety profile in this patient population assuming all options are available?

- Abiraterone: 20% (20 votes)
- Apalutamide: 6% (6 votes)
- Darolutamide: 50% (49 votes)
- Enzalutamide: 2% (2 votes)
- Any of the above: 22% (22 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

3.6.4. Management of side effects of AR antagonist monotherapy

The recently published phase 3 EMBARK trial in non-metastatic HSPC revitalised interest in AR antagonist monotherapy in advanced PC [99] (see also Section 3.2). In EMBARK, 45% of patients reported gynaecomastia (0.3% grade 3). Nipple pain was reported by 15.3% and breast tenderness by 14.4% of the patients [99]. No prophylactic RT or drug therapy was included as part of the trial design. Smaller trials of ARPI monotherapy (enzalutamide, apalutamide, and darolutamide) reported gynaecomastia in 35–55% and nipple pain in 6.5–41% of patients [294–298].

Historically, it was well known that monotherapy with nonsteroidal antiandrogens such as bicalutamide and flutamide results in gynaecomastia and mastodynia via a feedback loop that elevates the secretion of luteinising hormone (LH) [299–301]. Elevated LH levels stimulate testosterone production, which is subsequently converted to oestrogen via peripheral aromatisation. Since the AR is blocked by nonsteroidal antiandrogens, the increased oestrogen levels activate oestrogen receptors in breast tissue, promoting growth and resulting in gynaecomastia and/or breast pain in up to 70% of patients [299,301]. The rate of gynaecomastia with ADT alone is much lower because of the low level of testosterone and lack of conversion from testosterone to oestrogen.

For bicalutamide-induced gynaecomastia and/or mastodynia, a systematic review of 11 clinical trials concluded that these side effects can be effectively managed with prophylactic oral tamoxifen (10–20 mg daily) or RT without causing relevant side effects. Prophylaxis is more effective than treatment at the onset of gynaecomastia, and tamoxifen is a more effective preventative measure than RT [300,301]. Another effective management option for bothersome symptomatic gynaecomastia is surgery in the form of subareolar mastectomy.

7Q172: For the majority of patients who receive enzalutamide or bicalutamide monotherapy (150 mg OD), do you recommend a primary prophylaxis for gynaecomastia?

- Yes, breast bud irradiation: 46% (46 votes)
- Yes, tamoxifen: 5% (5 votes)
- Yes, subareolar mastectomy: 0% (0 votes)
- No: 49% (48 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

Q173: For the majority of patients who receive enzalutamide or bicalutamide monotherapy (150 mg OD) and who develop relevant gynecomastia, what further investigations do you recommend?

- Ultrasound: 32% (32 votes)
- Mammography: 15% (15 votes)
- None: 53% (52 votes)
- Abstain/unqualified to answer (7 votes)

No consensus.

Q174: For the majority of patients who receive enzalutamide or bicalutamide monotherapy (150 mg OD) and who develop bothersome gynecomastia, what is your preferred treatment?

- Breast bud irradiation: 24% (24 votes)
- Surgery: 26% (26 votes)
- Medical therapy (eg, tamoxifen): 18% (18 votes)
- None of the above, supportive measures (including drug discontinuation): 32% (33 votes)
- Abstain/unqualified to answer (5 votes)

No consensus.

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Q175: For the majority of patients who receive enzalutamide or bicalutamide monotherapy (150 mg OD) and who develop bothersome mastodynia, what is your preferred treatment?

- Breast bud irradiation: 26% (25 votes)
- Surgery: 6% (6 votes)
- Medical therapy (eg, tamoxifen): 29% (28 votes)
- None of the above, supportive measures (including drug discontinuation): 39% (38 votes)
- Abstain/unqualified to answer (9 votes)

No consensus.

Q176: Is it appropriate to extrapolate the data generated with bicalutamide 150 mg on prophylaxis of gynaecomastia to the AR antagonists (Apa, Daro, Enza)?

- Yes: 63% (62 votes)
- No: 37% (36 votes)
- Abstain/unqualified to answer (8 votes)

No consensus.

3.6.5. Discussion of side effects of systemic therapy and ARPI selection in special situations

Supplementary Figure 6 provides graphical representations of the voting results for questions on the side effects of systemic therapy and ARPI selection in special situations.

The long-term consequences of hormonal treatments are often underestimated and/or underaddressed by clinicians, especially because treatment advances for high-risk and locally advanced or metastatic disease have significantly prolonged both OS and the duration of exposure to hormonal therapies [269]. These evolutions in the disease trajectory make it crucial to consider potential side effects.

Similar to APCCC 2022, only a minority of panellists indicated that they would conduct a cardiac risk evaluation, an ECG, or a more thorough cardiac assessment before initiating ADT or ADT + ARPI for the majority of patients [4]. However, combining voting results for individual answer options often suggested a consensus in favour of recommending cardiac risk evaluations, at least for selected patients. This is noteworthy considering the established link between hormonal therapies and MACE and the fact that pivotal trials of newer hormonal treatments imposed stringent cardiac eligibility criteria. There also was consensus on the use of a simple measure such as blood pressure assessment in patients starting on ADT + abiraterone (strong consensus) or ADT plus an AR antagonist. Considering that a baseline cardiac evaluation such as ECG is recommended by professional societies such as the EAU [73], it is notable that APCCC panel members did not vote for such evaluations for most patients. Increasing the awareness of clinicians of the cardiovascular risks of long-term ADT-based regimens is important and will hopefully lead clinicians to consider preventive measures for more patients in the future. For patients on long-term ADT, individual assessment of cardiovascular risk can be performed using readily available online tools such as U-prevent (https://u-prevent.com/calculators) and specific mitigation measures can then be implemented, depending on individual risk factors.

At APCCC 2024, a discussion of where to refer patients for cardiac evaluations led to a pragmatic suggestion to hand patients an instruction card that outlines recommended examinations, similar to the cards given to patients who undergo cardiac valve replacement. To streamline resources, the patient's general practitioner could then perform a basic cardiovascular examination and refer patients to cardiology if they have abnormal test results or elevated risk of cardiac complications.

Guidelines developed by the cardio-oncology task force of the European Society of Cardiology (ESC) in collaboration with the European Haematology Association, ESTRO, and the International Cardio-Oncology Society include specific recommendations for patients with PC who require treatment with ADT [238]. These recommendations include a baseline cardiovascular risk assessment for patients without pre-existing cardiovascular disease (class I level B), consideration of a gonadotropin-releasing hormone (GnRH) antagonist for patients with pre-existing cardiovascular disease (class IIa level B), and an annual cardiovascular risk assessment in each year that patients are on ADT (class I level B). In addition, baseline and serial ECGs are recommended for patients at known risk of QTc prolongation (class I level B).

There was no consensus regarding drug therapy for bothersome hot flushes, and a relevant proportion of panellists abstained from voting on this topic, even though all have prescribed ADT and thus should have experience with this side effect. This discrepancy demonstrates ongoing uncertainty in this area. At ASCO 2024, which took place after APCCC 2024, investigators reported results from a randomised phase 2 study in which oxybutynin therapy significantly improved hot flush scores and frequency in comparison to placebo [275]. Other trials of various approaches, including fezolinetant, are planned or ongoing.

When asked about ARPI selection in special situations, panellists did not reach a consensus on a specific ARPI, but the majority voted for darolutamide. For these questions, the panel members were asked to assume that all options are available without restrictions. Ongoing trials of darolutamide in frail patients (eg, PEACE-6) will generate important evidence on this topic. Until such data are available, clinicians should refer to general guidelines and specific recommendations such as those from the International Society for Geriatric Oncology [302]. Of note, approval and reimbursement for different ARPIs may vary geographically. There is currently no high-level evidence that doublet therapy with darolutamide + ADT or triplet therapy with darolutamide + ADT + docetaxel improves outcomes over ADT alone in these select patient populations. Furthermore, there are no phase 3 clinical trial data on darolutamide for the treatment of M1 CRPC.

Voting by APCCC panellists on the management of patients on ARPI monotherapy suggests that that they currently have limited experience outside the clinical trial setting. The literature indicates high rates of gynaecomastia and mastodynia that could probably be prevented by pro-

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phylactic breast-bud irradiation (1–3 fractions only). There are no data on the proportion of patients in EMBARK who stopped therapy because of relevant gynaecomastia and associated symptoms. For patients with mastodynia, the literature on bicalutamide suggests that tamoxifen may be an effective treatment option; however, there are some concerns about longer-term use of tamoxifen in patients with advanced PC because of additional side effects, drug-drug interactions, and the effect of oestrogen receptor signalling on PC cell growth [303–305]. It is important to recognise that gynaecomastia and mastodynia are relevant side effects of AR antagonist monotherapy and should be discussed with patients before they start treatment.

3.7. Bone protection in advanced PC

3.7.1. HSPC

Treatment-related bone loss is a longstanding issue for patients with PC receiving hormonal treatments. ADT reduced bone mineral density (BMD) at an estimated rate of 2–8% per year; such cancer treatment–induced bone loss significantly increases the risk of fracture [250,269,306,307]. Furthermore, addition of an ARPI to ADT may increase the risk of osteoporotic fractures in comparison to ADT alone [283,284,308]. The risk of fracture can be reduced by use of bone-protecting agents (BPAs). The ESMO guidelines also recommend calcium and vitamin D supplementation, exercise, smoking cessation, and limiting alcohol intake for all patients undergoing long-term ADT [309]. In addition, BPA therapy at the dose and schedule indicated for prevention of cancer treatment–induced bone loss (eg, denosumab 60 mg every 6 mo or zoledronic acid 5 mg every 12 mo) is recommended for patients with a dual-energy X-ray absorptiometry (DEXA) T score <−2.0 and/or at least two of the following risk factors: age >65 yr; T score <−1.5; current or former smoker; body mass index <24 kg/m^2; family history of hip fractures; personal history of fragility fracture at age >50 yr; and oral glucocorticoid use for >6 mo [309]. Many patients with PC fulfil at least two of these criteria and thus would not necessarily need a DEXA scan in order to have an indication for initiation of BPA therapy. Although web-based tools such as the Fracture Risk Assessment Tool (FRAX) were not specifically developed for patients on ADT and hence do not currently account for bone loss induced by cancer treatment, they remain a valuable way for clinicians to assess risk factors for fracture and calculate individual risk. The current EAU guidelines strongly recommend that patients starting long-term ADT should be offered a DEXA scan to assess baseline BMD, with repeat measurements every 2 yr if antiresorptive therapy has not been initiated [73]. For patients with a DEXA T score <−2.5 or additional risk factors (similar to those mentioned above) that increase annual bone loss by more than 5%, the EAU guidelines strongly recommend offering a BPA [73].

The panel voted on several questions regarding osteoprotective therapy in patients with mHSPC.

Q177: In patients with mHSPC on long term continuous ADT-based therapy, do you recommend initiating therapy for prevention of cancer treatment induced bone loss other than calcium, vitamin D3 and exercise?

- Yes, in the majority of patients: 40% (42 votes)
- Yes, in selected patients (eg, according to ESMO or NCCN guidelines or bone mineral density scan): 58% (60 votes)
- No: 2% (2 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 98% voted in favour of antiresorptive therapy, at least in selected patients.

Q178: If you recommend antiresorptive therapy in a patient with mHSPC on continuous ADT-based therapy, what do you recommend?

- Denosumab 60mg q6 months subcutaneously: 62% (58 votes)
- Bisphosphonate q12 months intravenously: 21% (20 votes)
- Oral bisphosphonate: 17% (16 votes)
- Abstain/unqualified to answer (including I do not recommend antiresorptive therapy in these patients) (12 votes)

No consensus.

Patients with high-risk localised/locally advanced PC who are treated with ADT and an ARPI for 2–3 yr are at risk of not subsequently reaching full testosterone recovery or doing so only with some delay after stopping systemic therapy [310–312]. The panel voted on two questions related to this scenario.

Q179: In patients with high-risk localised/locally advanced prostate cancer on ADT-based therapy for 2–3 years, do you recommend initiating therapy for protection of cancer treatment induced bone loss other than calcium, vitamin D3 and exercise?

- Yes, in the majority of patients: 29% (30 votes)
- Yes, in selected patients (eg, according to ESMO or NCCN guideline or bone mineral density scan): 61% (63 votes)
- No: 10% (11 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 90% voted in favour of antiresorptive therapy, at least in selected patients.

Q180: If you recommend antiresorptive therapy in a patient with high-risk localised/locally advanced prostate cancer on ADT based therapy for 2–3 years, what do you recommend?

- Denosumab 60mg q6 months subcutaneously: 56% (51 votes)
- Bisphosphonate q12 months intravenously: 22% (20 votes)
- Oral bisphosphonate: 22% (20 votes)
- Abstain/unqualified to answer (15 votes)

No consensus.

In contrast to bisphosphonates, denosumab is not incorporated into the bone matrix, and bone turnover is not sup-

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pressed after its cessation. Patients who discontinue denosumab have a higher risk of new or progressing vertebral fractures due a rebound effect on bone resorption [313–315]. To help in averting this risk, a consolidating dose of a bisphosphonate has been suggested for patients stopping denosumab [316–318]. In a small case series of patients with nonmetastatic PC who were on denosumab, average bone loss of 2–5% occurred after denosumab was stopped [318].

A recent review summarising data for oncological patients concluded that although current evidence on denosumab transition regimens is based on individuals with osteoporosis, strategies proposed for these patients can be used to guide the management of cancer patients until more extensive direct evidence is available for these populations [319].

Q181: For the majority of patients with HSPC on denosumab (2×/year) who have to stop treatment with denosumab, do you recommend a consolidating dose of zoledronic acid to prevent bone loss upon discontinuation of denosumab?

- Yes, in the majority of patients: 34% (28 votes)
- Yes, but only in selected patients: 23% (19 votes)
- No: 43% (36 votes)
- Abstain/unqualified to answer (including I do not recommend denosumab in this situation) (23 votes)

No consensus.

3.7.2. *mCRPC*

Regarding disease-related skeletal complications, randomised trials have demonstrated a reduction in SREs and symptomatic SREs (SSEs) with addition of denosumab (120 mg subcutaneously every 4 wk) or zoledronic acid (4 mg intravenously every 4 wk), respectively, to SOC treatment [320–322]. However, both of these agents are associated with higher risk of osteonecrosis of the jaw, a well-recognised adverse event that increases in likelihood with cumulative doses [323]. Previous APCCCs frequently failed to reach consensus on questions related to bone-targeting agents for patients with mCRPC [1–4], although many panellists at APCCC 2019 voted in favour of bone-protective therapy for patients with mCRPC and bone metastases (65% for the majority of cases, 22% for selected patients only) [2]. Relevant factors for patient selection might encompass overall prognosis, number of bone metastases, and dental health status.

Specifically, consensus at prior APCCCs remained elusive regarding the preferred duration and frequency of denosumab and zoledronic acid administration at the dosages recommended for averting SREs in the majority of patients with mCRPC. Two trials are currently investigating reduced-frequency treatment schedules for bone-targeting agents. A large, randomised, phase 3 noninferiority trial (REDUSE; NCT02051218) in patients with mCRPC or bone-metastatic breast cancer is investigating a reduced-frequency denosumab schedule after an initial monthly run-in phase, for which the primary endpoint is time to first SSE; this trial has completed recruitment but has not yet reported results [324]. A smaller trial (REaCT-BTA) randomised patients with mCRPC or metastatic breast cancer to receive denosumab, pamidronate, or zoledronic acid every 4 wk or every 12 wk, for which the primary endpoint was the change in health-related quality of life [325]. The 2-yr SSE rates were 32.7% in the 4-weekly arm and 28.1% in the 12-weekly arm, and a post hoc analysis revealed that on-study SSEs in the 12-weekly dosing arm were associated with a small, nonsignificant increase in the risk of subsequent SSEs [326]. In another randomised trial in patients with metastatic breast cancer, PC, or multiple myeloma, zoledronic acid administered every 12 wk was noninferior to zoledronic acid at the standard dosing interval of every 4 wk for the primary outcome of the proportion of patients with at least one SRE within 2 yr of randomisation [327].

At APCCC 2024, panellists voted on their preferred dose, frequency, and treatment duration for bone-targeting agents for patients with mCRPC.

Q182: For the majority of patients with mCRPC and bone metastases, what do you recommend regarding dose/frequency when starting of bone-targeting agents?

- Monthly administrations: 52% (48 votes)
- Three monthly administrations (± loading phase): 48% (44 votes)
- Abstain/unqualified to answer (14 votes)

No consensus.

Q183: For the majority of patients with mCRPC and bone metastases on monthly denosumab or zoledronic acid, what do you recommend in the absence of toxicity?

- Stop bone-targeting agent after 2 years: 30% (26 votes)
- Continue bone-targeting agent after 2 years and reduce frequency of administration: 62% (54 votes)
- Continue bone-targeting agent monthly also after 2 years: 8% (7 votes)
- Abstain/unqualified to answer (19 votes)

No consensus.

A combined total of 92% voted in favour of stopping or reducing the administration frequency of bone-targeting agents after 2 yr.

3.7.3. *Discussion on bone protection in PC*

Supplementary Figure 7 provides graphical representations of the voting results for questions on bone protection in PC.

With regard to treatment-induced bone loss, panellists seemed to show greater awareness of the importance of bone protection in patients with high-risk localised PC, locally advanced PC, or mHSPC who are on long-term ADT, with almost all panel members voting in favour of BPA treatment, at least in selected patients. This approach is also recommended by expert guidelines. Individual patient risk factors, online risk assessment tools, and DEXA scans (if available) can help clinicians in assessing the risk of fracture to guide their decisions on offering BPA therapy.

For patients with nonmetastatic PC, APCCC 2024 did not address the question of whether testosterone recovery should be factored into decisions on stopping BPA therapy.

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However, from a theoretical standpoint, it does not appear to make sense to stop BPA therapy if testosterone remains at a castrate level despite hormonal treatment having been discontinued.

For patients with mHSPC starting ADT plus an ARPI, only 19% of the APCCC 2022 panellists voted in favour of recommending BPA treatment for the majority of patients, while 40% of the APCCC 2024 panellists voted for this answer option. This increase may be because of recent evidence showing that the higher risk of fracture in patients receiving hormonal therapies is often independent of T scores, as ADT causes not only a quantitative reduction but also a qualitative change in bone mass [269,328,329]. A post hoc analysis of STAMPEDE data revealed that zoledronic acid given in the hormone-sensitive setting significantly reduced the risk of fracture-related hospitalisations; the authors concluded that these results support the use of zoledronic acid to reduce the risk of fracture in patients with mHSPC [330]. Results from these studies suggest that all patients receiving continuous hormonal therapy should be evaluated for possible BPA therapy.

For the mCRPC setting, almost half of the panellists voted in favour of starting BPA therapy upfront at a lower frequency of once every 3 mo, even though the data showing a benefit of BPA therapy are from studies in which patients were treated monthly, and thus far there are only limited clinical trial data in support of reducing the dosing frequency. Interestingly, the vast majority of panellists voted in favour of either stopping bone-targeting agents after 2 yr or reducing the administration to every 3 mo in patients with mCRPC. This decision should probably be influenced by clinical factors such as the response to systemic therapy, the extent of bone metastatic disease, and dental status.

3.8. *Genetics and genomics*

Both the EAU and NCCN guidelines recommend pursuing germline genetic (hereditary) and somatic (genomic or tumour-specific) testing for patients who have high-risk features, a family and/or personal history of cancer or Ashkenazi Jewish ancestry, and/or metastatic PC [7,73]. The EAU guidelines recommend tumour genomic (ie, somatic) testing in the mCRPC setting [73], whereas the NCCN guidelines recommend this in the earlier mHSPC setting [7]. Importantly, while tumour somatic test results may prompt confirmatory germline testing, they should not entirely be relied on to identify pathogenic germline alterations, as these can be missed by somatic testing alone [331–334]. Thus, a comprehensive evaluation requires both germline and somatic tests [335].

Knowledge of HRR gene alterations (germline and/or somatic) have an impact on treatment decisions for patients with mCRPC. The PARP inhibitors olaparib and rucaparib can be administered to patients who previously received an ARPI, and HRR gene alterations affect decisions on the use of ARPI + PARP inhibitor combinations, although the specifics differ according to the regulatory approval status in different countries and geographic regions (see Section 3.4).

To date, there are no prospective data on how genetic and genomic tests should influence the management of patients with mHSPC or locally advanced PC. A number of ongoing studies in mHSPC are attempting to address these questions (AMPLITUDE, NCT04497844; TALAPRO-3, NCT04821622; EvoPAR-PR01, NCT06120491; and STAMPEDE2, NCT06320067), as well as several studies in the neoadjuvant setting (GUNS, NCT04812366; NePtune, NCT05498272; and S2210, NCT05806515).

APCCC 2024 panellists voted on questions relating to the use of genetic tests for locally advanced PC, mHSPC, and mCRPC.

Q99: For the majority of patients with high-risk localised/locally advanced prostate cancer, do you routinely recommend genetic evaluation (germline and/or somatic)?

- Yes, germline testing: 30% (31 votes)
- Yes, somatic testing plus/minus germline testing only in case of relevant somatic alterations: 14% (15 votes)
- Yes, both germline and somatic testing, independent of findings in somatic testing: 21% (22 votes)
- No: 35% (37 votes)
- Abstain/unqualified to answer (1 vote)

No consensus.

Q100: For the majority of patients with mHSPC, do you routinely recommend genetic evaluation (germline and/or somatic) (if not performed earlier)?

- Yes, germline testing: 16% (16 votes)
- Yes, somatic testing plus/minus germline testing only in case of relevant somatic alterations: 25% (26 votes)
- Yes, both germline and somatic testing, independent of findings in somatic testing: 42% (44 votes)
- No: 17% (18 votes)
- Abstain/unqualified to answer (2 votes)

No consensus.

A combined total of 83% voted in favour of some form of testing.

Q101: Outside a clinical trial, does the information of genetic evaluation (germline and/or somatic) influence your decision for first-line treatment of mHSPC in the majority of patients (if testing is available without restrictions)?

- Yes: 24% (24 votes)
- No: 76% (78 votes)
- Abstain/unqualified to answer (4 votes)

Consensus that the information from genetic evaluation does not influence the decision on first-line treatment for mHSPC in the majority of patients.

Q102: Outside a clinical trial, does the information of genetic evaluation (germline and/or somatic) influence your decision for first-line treatment of mCRPC in the majority of patients (if testing is available without restrictions)?

- Yes: 80% (81 votes)
- No: 20% (20 votes)
- Abstain/unqualified to answer (5 votes)

Consensus that the information from genetic evaluation influences the decision on first-line treatment for mCRPC in the majority of patients.

Q103: For the majority of patients with mCRPC, do you routinely recommend genetic evaluation (germline and/or somatic) (if not performed earlier)?

- Yes, germline testing: 0% (0 votes)
- Yes, somatic testing and germline testing only in case of relevant somatic alterations: 36% (37 votes)
- Yes, both germline and somatic testing, independent of findings in somatic testing: 59% (61 votes)
- No: 5% (5 votes)
- Abstain/unqualified to answer (3 votes)

No consensus.

A combined total of 95% voted in favour of some form of testing.

3.8.1. Discussion on genetics and genomics

Supplementary Figure 8 provides graphical representations of the voting results for questions on genetics and genomics.

Although no consensus was reached, the majority of panellists recommended somatic and/or germline testing in patients with locally advanced and metastatic HSPC (65% and 73%, respectively). There was no consensus on whether to perform germline or somatic tests or both, but the proportion of panel members voting for a combination of both testing strategies was only 21% for locally advanced PC versus 59% for mCRPC. The absence of consensus may reflect variations in guidelines, test coverage/availability, genetic counselling resources, and requirements in different countries and practice settings. We hope and envision that this will change, that testing will become more widely available and affordable, and that resulting clinical decisions and treatment options will be better defined. Testing is also important because results are informative for patients and families with regard to hereditary cancer risk and clinical trial eligibility.

According to APCCC 2024 panellists, information from genetic evaluations should currently influence therapeutic decisions on first-line treatment of mCRPC but not mHSPC. This reflects positive results from recent phase 3 studies of ARPI + PARP inhibitor combinations for first-line treatment of mCRPC (PROpel, MAGNITUDE, and TALAPRO-2) and PARP inhibitor monotherapy (PROfound, TRITON3). We await final results from similar trials in the mHSPC setting (the ongoing AMPLITUDE, TALAPRO-3, and EvoPAR-PR01 trials), and thus the panel voted against using genetic test results to guide treatment for these patients at this time. There is also ongoing research on whether genomics can help in guiding decisions on the use of doublet versus triplet systemic therapy for mHSPC. Further discussion is needed to determine the optimal timing of germline testing to maximise family cascade testing and identify the impact on public health.

4. Discussion

The APCCC forum offers a unique platform for gathering the opinions of a panel of renowned PC experts who convene to discuss and vote on unresolved questions that current literature and guidelines may be unable to address owing to a lack of high-level evidence. It is not surprising, therefore, that panellists did not reach consensus on many of the questions, since they intentionally focus on areas that lack prospective data. A separate manuscript discussing knowledge gaps identified at APCCC 2024 and how best to address them is in preparation.

While this report captures current expert opinions, it should be interpreted and integrated into clinical practice with the same scrutiny applied to any major publication, recognising that consensus does not equate to or replace evidence and is in fact the lowest level of evidence. Areas of consensus simply reflect a high level of current agreement among experts and (in some cases) the evolution of expert perspectives in response to new data and diagnostic and therapeutic approvals. For questions on which panellists reached consensus, it is important not to assume that their opinion is correct—it may well be that the results of one or more future randomised trials on the topic prove a consensus opinion to be wrong.

It is equally essential to understand that the results of APCCC voting reflects experts' current views that are based on their clinical experience and understanding of the literature and available evidence. For example, while panellists were asked to assume that all diagnostic and therapeutic options were available without restrictions, some voting results may reflect limited experience with newer tests and modalities, such as next-generation imaging and genomic tests; panellists who have not yet worked with these advances may be hesitant to endorse their use.

In addition, for many health care providers globally, diagnostic and therapeutic options may be limited in availability or cost coverage. In reality, health care budgets cannot cover all diagnostic and therapeutic options for all patients with advanced PC, regardless of results from evidence-based studies. Consequently, health care providers often face dilemmas related to treatment access for their patients. Limited resources necessitate careful allocation, which impacts care access. From a global perspective, it is essential to balance resource use in order to benefit as many patients as possible, minimise waste, and address treatment disparities. A recently published report from the Lancet Commission on Prostate Cancer projects that the number of new PC cases will rise from 1.4 million in 2020 to 2.9 million by 2040 [336], underscoring the increasing importance of optimal use of the technologies available. To achieve this goal, regulatory agencies strive to only approve treatments that demonstrate a favourable cost-effectiveness profile so that clinicians can recommend appropriate treatments, and treatments that offer an insufficient benefit relative to their cost are deemed wasteful and not made available. Nonetheless, some APCCC voting results may be helpful in supporting the regulatory approval of certain treatment options or diagnostic procedures. A case in point is the APCCC 2024 consensus vote on performing tumour genomic profiling

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for mCRPC cases before considering the use of a PARP inhibitor. Such individualised approaches may improve the likelihood of achieving favourable treatment outcomes while avoiding unnecessary health care costs.

5. Conclusions

We expect that the APCCC will directly address topics such as resource allocation in the future and will seek expert consensus and identify high-priority gaps in guidelines, policies, and clinical practice. As clinicians and researchers, we must also ensure that clinical trials are conducted correctly and with equipoise in relation to SOC control arms, which helps in maximising the quality of the data generated. Finally, we note that the expert panel largely comprised highly specialised clinicians practicing mostly in tertiary cancer centres around the world. In comparison to this group of experts, community-based physicians may see a larger proportion of frail and older patients, so some of these consensus statements may not apply to many of their patients.

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