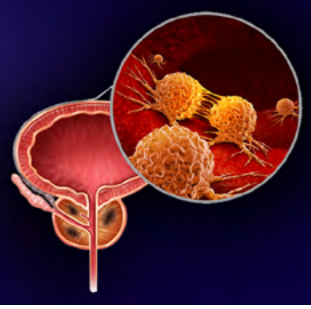
Prostate Cancer Practice Review™



Making Education Easy

Issue 13 - 2023

In this issue:

Abbreviations used in this issue:

AAP = abiraterone acetate plus prednisone; **ADT** = androgen deprivation therapy; **ARTA** = androgen receptor-targeting agent; **AUA** = American Urological Association; **CT** = computed tomography; **CRPC** = castration-resistant prostate cancer; **EAU** = European Association of Urology; **HR** = hazard ratio; **HRR** = homologous recombination repair; **HSPC** = hormone-sensitive prostate cancer; **LHRH** = luteinizing hormone-releasing hormone; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **PARP** = poly (adenosine diphosphate [ADP]-ribose) polymerase; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **SBRT** = stereotactic body radiation therapy.

Welcome to the 13th issue of Prostate Cancer Practice Review.

This Review covers news and issues relevant to clinical practice in prostate cancer. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Clinical Practice

European PRAISE-U project evaluates novel risk-adapted screening for prostate cancer

PRAISE-U (PRostate cancer Awareness and Initiative for Screening in the European Union), a European program that aims to configure and implement a cost-effective smart early detection prostate cancer algorithm across the continent, has launched with an event in Belgium in April 2023, following EU4Health approval.

With the noble goal of transforming the traditional screening paradigm from a universal digital rectal examination, elevated prostate-specific antigen (PSA) plus prostate biopsy strategy to a customised risk-based approach with nation-specific tailoring, the overarching objective of the program is to improve prostate cancer-related morbidity and mortality while minimising overdiagnosis and unnecessary treatment.

The pan-European initiative will run for three years until April 2026 and entails a multi-disciplinary consortium comprised of clinicians, researchers, and policy makers from 25 institutions including hospitals, medical societies and national authorities in 12 countries that will collaboratively extend the current EU guidance for screening developed in other cancer indications through projects like CanScreen 5 and EU-TOPIA, to prostate cancer. Smart early-detection risk-based programs will commence initially in five pilot sites in Lithuania, Ireland, Poland, the Galicia Region of Spain and Manresa, Spain and if demonstrated to be effective, feasible, acceptable and cost-effective, further rolled-out or refined and adapted with the aim of risk-adapted prostate cancer screening throughout Europe from 2027. In addition, a central online interactive knowledge resource will be established as a repository for large-scale data, enabling relevant analysis, and to coordinate workshops, conferences, publications, reports and guidelines.

The proposed risk-adapted approach involves a four-step screening process with only men deemed to be at intermediate-risk or high-risk proceeding to each subsequent step to avoid unnecessary tests in men with indolent cancer, and early diagnosis before establishment of incurable disease in men with significant malignancy as follows:

- PSA testing in high-risk groups according to age as follows:
  - men over 50 years of age
  - men over 45 years of age with a family history of prostate cancer or who are of African descent
  - men over 40 years with *BRCA2* variants
- Clinical assessment considering family history, prostate volume, PSA density, urinary symptoms *inter alia*
- Multi-parametric MRI scan to calculate PIRADS score
- Biopsy, preferably transperineal

Results from this program are eagerly awaited.

Download the full press release here

PROBASE: digital rectal examination is not useful as a solitary screening tool for prostate cancer in young men

Population-based PSA screening is controversial with advocates citing the very real survival advantages of enhanced detection and earlier treatment, while critics/opponents worry that the rates of overdiagnosis caused by the poor specificity of elevated PSA to distinguish between malignancy and other conditions such as benign prostatic enlargement or prostatitis (only one-quarter of men with a raised PSA levels have prostate cancer), as well as its inability to identify aggressive disease requiring immediate treatment from indolent tumours, results in overtreatment with long-term side effects including erectile dysfunction/impotence and impaired continence.

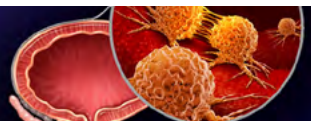
To date, the German national preventative screening program for prostate cancer only subsidises digital rectal examinations, not PSA testing, for men 45 years or older, a test reliant on tumours being physically accessible and large enough to be palpable and thus, frequently already spreading to neighbouring organs.

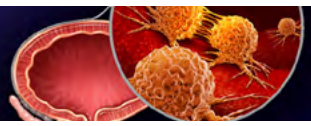
The ongoing German PROBASE risk-based screening study is evaluating an approach stratified by baseline PSA value at the age of 45 years to improve screening. Briefly, over 46 thousand men were accrued to the trial between 2014 and 2019 from four university sites in Munich, Hannover, Heidelberg and Düsseldorf and randomised to undergo immediate PSA testing or digital rectal exam with delayed PSA screen at 50 years of age.

Results from PROBASE were presented during the 38th annual European Association of Urology (EAU) Congress in March in Italy. The new data reconfirmed previous findings of inferior prostate cancer detection with digital rectal examination only versus PSA testing from a preliminary analysis of the first screening round presented at EAU 2021. The researchers reported that while the prevalence of prostate cancer, especially unfavourable disease, is very low in this age group overall, digital rectal exam detected roughly four-fold fewer cases compared to PSA testing and is therefore, not a robust screening approach when used in isolation. Whether the low screening rates in Germany, with less than one-fifth of eligible men undergoing testing, could be improved by less invasive testing such as PSA or MRI is also relevant to policy decision making.

While the contentious issue continues to be debated and several novel screening paradigms are undergoing investigation, it is clear that identification of further prostate cancer tumour markers in serum or urine to pair with PSA quantification would aid in diagnostic specificity.

Eur Urol. 2023;83(Supplement 1- Abstract A0899): S1282-83





Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023)

The AUA and SUO have complied a 2023 Guideline Amendment to the 2020 Advanced Prostate Cancer guideline. Based on a comprehensive literature review including evidence from 16 key studies plus other authenticated standards of care that have evolved since the last iteration, updates have been made to 23 of the 38 original evidence and consensus-based statements across the four advanced prostate cancer disease states. No overhaul of the sections titled, "Early Evaluation and Counselling" or "Bone Health" was deemed necessary, with the exception of a supporting note to advocate for inclusion of a mental health expert in the multidisciplinary care team. Finally, the publication discusses future directions in this field including advanced PET imaging and theranostics, metastasis-directed therapy, biomarkers and other systemic therapies and unmet needs. This document provides up-to-date evidence-based information and is a valuable resource for clinicians treating patients with advanced prostate cancer to optimise the quality of care.

A précis of the Advanced Prostate Cancer Algorithm with updates identified by italics is herein:

Biochemical recurrence without metastatic disease after exhaustion of local treatment options

- Prognosis
  - Inform patients regarding the risk of metastasis and follow patients with serial PSA measurements and clinical evaluation
  - Perform periodic staging evaluations in patients at higher risk for the development of metastases consisting of cross-sectional imaging (computed tomography [CT], MRI) and technetium bone scan, *and/or preferably prostate-specific membrane antigen (PSMA) PET imaging* (with (^{68}Ga-PSMA-11 or Piflufolastat F-18 [^{18}F-DCFPyl])
  - *Utilize PSMA PET imaging preferentially, where available, as an alternative to conventional imaging, or in the setting of negative conventional.* Radiographic assessments based on overall PSA and PSA kinetics may be considered
- Treatment
  - *Offer observation or clinical trial enrolment.* Clinicians should not routinely initiate androgen deprivation therapy (ADT) but weigh up the benefits of systemic therapy with the impact of adverse events and quality of life. If ADT is initiated, intermittent in lieu of continuous dosing may be an option

Metastatic hormone-sensitive prostate cancer (HSPC)

- Prognosis
  - *Assess the presence, extent and precise locations of metastatic disease and related symptoms*
  - *Offer germline testing, and consider somatic testing and genetic counselling*
  - Obtain a baseline PSA and serial PSAs at three- to six-month intervals after ADT initiation and consider periodic imaging
- Treatment
  - Offer ADT with either luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or surgical castration
  - *Offer ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel).*
  - *Select patients with de novo mHSPC can be offered ADT in combination with docetaxel and either abiraterone acetate plus prednisone, or darolutamide.*
  - Select patients with low-volume metastatic disease may be offered primary radiotherapy to the prostate
  - First generation antiandrogens plus LHRH agonists should only be used to block testosterone flare, and oral androgen pathway directed therapy should not be used without concurrent ADT

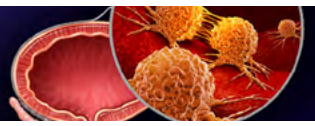
Non-metastatic CRPC

- Prognosis
  - Obtain serial PSA measurements at three- to six-month intervals and calculate PSA doubling time from development of castration resistance
  - *Assess for development of metastatic disease using conventional or PSMA PET imaging at intervals of six to 12 months.*
- Treatment
  - Offer apalutamide, darolutamide or enzalutamide with continuing ADT to patients at high risk for developing metastatic disease. Observation with continued ADT may be recommended, particularly for patients at lower risk for metastasis. Systemic chemotherapy or immunotherapy should NOT be offered outside the context of a clinical trial

Metastatic CRPC

- Prognosis
  - Obtain baseline labs and review locations of metastatic disease, disease-related symptoms and performance status
  - *Perform imaging at least annually in patients without PSA progression or new symptoms*
  - *Order PSMA PET imaging in patients with disease progression following docetaxel and androgen pathway inhibition considering ^{177}Lu-PSMA-617 therapy*
  - *Offer germline and somatic genetic testing if not already performed, to identify DNA repair deficiency, microsatellite instability status, tumour mutational burden, and other potential mutations that may inform prognosis and direct potential targeted therapies*
- Treatment
  - *In newly diagnosed patients who have not received prior androgen receptor pathway inhibitors, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide*
  - Offer radium-223 to patients with symptoms from bony metastases and without known visceral disease or lymphadenopathy > 3cm
  - *Offer ^{177}Lu-PSMA-617 to patients with progressive disease having previously received docetaxel and androgen pathway inhibitor with a positive PSMA PET imaging study*
  - Cabazitaxel should be recommended over other androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide
  - A PARP inhibitor should be offered to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutation following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy; platinum-based chemotherapy may be offered for patients who cannot use or obtain a PARP inhibitor
  - Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high metastatic CRPC. Sipuleucal-T may be offered to asymptomatic/minimally symptomatic patients

J Urol. 2023;209(6):101097



Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer

MAGNITUDE, an international phase 3 double-blind trial sponsored by Janssen Research & Development, enrolled 670 men with metastatic CRPC to investigate the addition of the PARP inhibitor niraparib to the standard of care regimen comprised of abiraterone acetate plus prednisone (AAP) in two cohorts according to HRR gene alteration status. Patients with/without HRR gene alterations (HRR-positive, n=423; HRR-negative, n=247) and imaging confirmed metastatic disease in the setting of castrate levels of testosterone (≤ 50 ng/dL on a gonadotropin releasing hormone analogue or following bilateral orchiectomy) were administered 28-day cycles of AAP ± niraparib (200 mg/day) until unequivocal clinical progression or prohibitive toxicity.

At a median follow-up of just over 18 months radiographic progression-free survival (PFS) per blinded independent central review in patients with *BRCA1/2* mutated disease was delayed by almost six months with the addition of niraparib to AAP, extending the median from 10.9 months to 16.6 months and halving the risk of disease progression or death compared to AAP alone (hazard ratio [HR] 0.53; p=0.001). Similarly, in the overall HRR biomarker-positive cohort - including patients with monoallelic or biallelic pathogenic HRR gene aberrations in *ATM, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2* and/or *BRCA1/2* - a significant benefit in terms of radiographic PFS was found in the niraparib arm with a 27% reduced risk of progression versus control (16.5 vs 13.7 months; HR 0.73; p=0.022). The benefit to inclusion of a PARP inhibitor in this population was restricted to patients with HRR gene alterations, with prespecified futility criteria met in the HRR negative cohort and enrolment to this cohort prematurely terminated by recommendation of an Independent Data Monitoring Committee. These findings were consistent in sensitivity analyses and across most prespecified subgroups. Other significant benefits in the niraparib arm included delays in time to symptomatic progression, and an approximate doubling of median time to PSA progression and objective response rates (HRR-positive cohort, 59.7% vs 28.1%; *BRAC1/2* cohort, 51.8% vs 31.3%). Survival data is immature. The combination regimen was deemed tolerable, with the most common grade ≥ 3 adverse events anaemia and hypertension.

Pending confirmation of translation of delayed disease progression into a clinically relevant survival benefit, niraparib plus AAP may be a new front-line option for HRR gene mutated metastatic CRPC, especially for patients with *BRCA1/2* mutations.

J Clin Oncol. 2023 Mar 23. Online ahead of print

Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer

The EXTEND (External Beam Radiation to Eliminate Nominal Metastatic Disease) phase 2 randomised clinical trial, a basket study assessing the addition of local consolidative therapy to standard systemic treatment in patients with a metastatic solid tumour, is a multi-centre US study sponsored by the M.D. Anderson Cancer Centre and being conducted in collaboration with the National Cancer Institute.

Recently reported results from the prostate cancer basket in men with oligometastatic disease who received intermittent ADT ± metastasis-directed radiotherapy indicate that the combination may improve oncologic outcomes and permit longer hormone treatment-free periods. Briefly, 87 men (median age 67 years) with no more than five metastases who had undergone two or more months of hormone therapy were accrued and assigned to hormone therapy with a LHRH agonist/antagonist with or without a second-generation androgen-receptor targeting agent (ARTA; n=43); or hormone therapy plus definitive radiotherapy to all sites of disease (n=44). Hormone therapy was administered for six months followed by a break until confirmed disease progression. At an almost two-year median follow-up the trial met the primary outcome measure of significantly delayed disease progression (radiographic, clinical or biochemical) with metastasis-directed radiotherapy plus hormone therapy to demonstrate superior efficacy versus hormone therapy alone (median PFS, not reached vs 15.8 months; HR 0.25). The addition of metastasis-directed radiotherapy also extended the time from recovery of eugonadal testosterone levels to progression (not reached vs 6.1 months; HR 0.32), reducing the side effects of hormonal therapy. Overall survival data are immature and will be reported separately.

JAMA Oncol. 2023 April 23. Online ahead of print

Magnetic resonance imaging–guided vs computed tomography–guided stereotactic body radiotherapy for prostate cancer. The MIRAGE randomised clinical trial

The first phase 3 randomised clinical trial of its kind, the MIRAGE (MRI-Guided Stereotactic Body Radiotherapy for Prostate Cancer) trial, conducted at the UCLA Jonsson Comprehensive Cancer Centre in the US, compared the treatment-related burden and acute tolerability of two imaging modalities for guided delivery of stereotactic body radiation therapy (SBRT) for prostate cancer - CT imaging and MRI. The trial was planned due to the recent availability of MRI-guided linear accelerators to deliver therapeutic radiation doses with smaller target volume margins, and hence more focussed treatment with reduction of inadvertent dosing to nearby organs such as the bladder and rectum.

A total of 156 men with a clinical localised adenocarcinoma of the prostate with no evidence of disease in pelvic lymph nodes or extrapelvic metastasis were accrued to the trial and underwent 40 Gy SBRT in five fractions with MRI- or CT-guidance (n=79 and n=77, respectively). A prespecified interim futility analysis with at least three months of follow-up revealed a significant reduction in the incidence of acute toxicity of at least moderate severity with MRI- versus CT-guided SBRT (24.4% vs 43.4%; p=0.01) and complete abrogation of gastrointestinal toxicity (0% vs 15.5%). Treatment-related lower urinary tract and bowel symptoms were also mitigated in the MRI-guided treatment cohort compared to the CT-guided cohort as assessed by changes in the International Prostate Symptom Score and Expanded Prostate Cancer Index Composite-26 (EPIC-26), respectively, at one-month post treatment.

Longer follow-up data from the trial will allow assessment of the durability of these effects and confirm oncological efficacy but these findings suggest that MRI-guided prostate SBRT is a substantially more tolerable option than CT-guided SBRT, affording faster recovery, which may justify the extra upfront cost of equipment and time investment.

JAMA Oncol. 2023;9(3):365-73

News in Brief

First-in-human, phase 1 study of PF-06753512, a vaccine-based immunotherapy regimen, in non-metastatic hormone-sensitive biochemical recurrence and metastatic castration-resistant prostate cancer

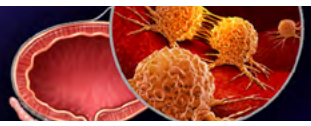
Autio et al report results from a phase 1 trial of a vaccine-based immunotherapy regimen in patients with different stages of prostate cancer. Patients with hormone-sensitive relapse after definitive local therapy (n=35) or progressive mCRPC (n=56) were included in dose escalation and dose expansion cohorts and received a median of two cycles consisting of replication-deficient adenovirus vector prime targeted to three prostate cancer antigens (PSMA, PSA and prostate stem cell antigen), boosts with plasmid DNA encoding the same antigens plus immunotherapy with antibodies targeting CTLA-4 (tremelimumab) ± anti-PD-1 (sasanlimab). Although this approach was immunogenic, low objective response rates were achieved (5.6% overall in mCRPC cohort overall; 16.7% in the cohort who received phase 2 recommended dosing) and toxicity was an issue with grade 3/4 treatment-related adverse events in 41.1% of patients and two deaths deemed treatment-related. The sponsor, Pfizer, terminated the trial and will not be evaluating this agent further.

J Immunother Cancer. 2023;11(3): e005702

Smoking and risk of prostate cancer and prostate cancer death

A pooled study from Sweden that included over 350 thousand men from five cohorts with over 20 years of follow-up analysed the incidence of prostate cancer according to smoking status and body mass index. Cox regression analysis revealed a marginally decreased risk of localised prostate cancer development in the age of PSA testing in smokers but conversely, a significantly higher risk of poor prognosis including a 10% to 20% elevated risk of dying from prostate cancer, regardless of tumour stage at diagnosis, with risk exacerbated by a high body mass index (HR 1.49). The authors attributed the lower risk of prostate cancer in smokers to low uptake of PSA screening.

Eur Urol. 2023;83(5):422-31



Combination treatment with sipuleucel-T and abiraterone acetate or enzalutamide for metastatic castration-resistant prostate cancer: STAMP and STRIDE Trials

Concurrent or sequential administration of the ARTAs AAP or enzalutamide with the dendritic cell-based vaccine sipuleucel-T for mCRPC does not adversely impact efficacy or immunogenicity, according to long-term follow-up results from STAMP and STRIDE. Kaplan–Meier estimates of overall survival with updated data remained at roughly 33 months in both trials, regardless of timing of ARTA administration. An immunologic prime-boost effect with elicitation of anti-PA2024 and anti-prostatic acid phosphatase immunoglobulins was also maintained when sipuleucel-T was part of a combination regimen.

Clin Cancer Res. 2023 Apr 14. Online ahead of print

Neoadjuvant enoblituzumab in localised prostate cancer: a single-arm, phase 2 trial

This single arm, open-label phase 2 trial, conducted at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Centre in Maryland in the US, evaluated the anti-tumour activity of the novel B7 homolog 3 (B7-H3) targeted immunotherapeutic enoblituzumab in operable localised prostate cancer. Men with intermediate or high-risk disease (clinical stage T1c-T3b) with no lymph node or other metastasis (n=32) received six doses of 15 mg/kg enoblituzumab prior to prostatectomy. Clinical activity was demonstrated with two-thirds of patients having undetectable PSA levels at one-year post-surgery and was well tolerated with grade 3 adverse events the most severe toxicity experienced and uncommon, reported in 12% of patients.

Nat Med. 2023;29(4):888-97

COVID-19 Resources

Clinical Oncology Society of Australia
Cancer Australia
The Royal Australian and New Zealand College of Radiologists
Royal Australasian College of Surgeons
European Urology Journal
British Association of Urological Surgeons
American Urological Association
European Society of Medical Oncology
American Society of Clinical Oncology

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MOGA – Events
USANZ – Events
COMS – Conferences and Meetings on Urology

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Prostate Cancer Research Review with Associate Professor Niall Corcoran and Professor Nathan Lawrentschuk

Urology Research Review with Professor Eric Chung

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