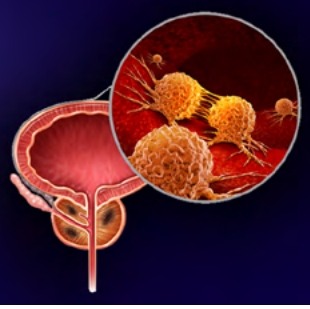
Prostate Cancer Practice Review™



Making Education Easy

Issue 20 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy; **AUA** = American Urological Association; **ASTRO** = American Society for Radiation Oncology; **CT** = computed tomography; **HR** = hazard ratio; **mCRPC** = metastatic castration-resistant prostate cancer; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **SUO** = Society of Urologic Oncology.

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Welcome to the 20th 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

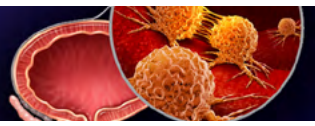
PRESTO: A phase III, open-label study of intensification of androgen blockade in patients with high-risk biochemically relapsed castration-sensitive prostate cancer (AFT-19)

The US multi-centre PRESTO trial evaluated intensification of fixed-duration androgen blockade with next-generation androgen pathway inhibitors in men with high-risk biochemically relapsed castration-sensitive prostate cancer, given the survival benefit demonstrated in the nonmetastatic castration-resistant and metastatic castration-sensitive treatment spaces. A total of 503 men with biochemically recurrent prostate cancer without evidence of metastases at high risk for the development of distant metastasis due to fast-rising prostate-specific antigen (PSA) levels (PSA > 0.5 ng/mL; PSA doubling time ≤ 9 months) after prior radical prostatectomy and adjuvant or salvage radiation for histologically confirmed prostate adenocarcinoma were enrolled into the three-arm trial and administered 12 months of standard androgen deprivation therapy (ADT) alone, or ADT plus apalutamide ± abiraterone acetate plus prednisone (AAP).

Results from the first planned interim analysis showed that compared to hormone injections alone both combination hormonal therapy approaches more durably suppressed PSA levels. The addition of apalutamide to ADT prolonged median PSA progression-free survival (PSA-PFS) by almost five months - from 20 months to 24.9 months (hazard ratio [HR] 0.52) - while the addition of apalutamide and AAP extended PSA-PFS by almost six months versus ADT (26 vs 20 months; HR 0.48). Consistent delays in PSA-PFS were observed regardless of baseline PSA doubling time (< 3 vs 3-9 months). Improvements in PSA control with more complete androgen receptor blockade did not come at the expense of delayed testosterone recovery at treatment termination, with comparable time to testosterone recovery (> 50 ng/mL) found across the three treatment arms.

While ADT plus apalutamide had a manageable safety profile with comparable rates of ≥ grade 3 adverse events and serious adverse events as ADT alone, greater toxicity was found with ADT plus apalutamide + AAP. Given this reduced tolerability plus the lack of signal of clinical benefit with the addition of AAP to ADT plus apalutamide (albeit the study was not powered to directly compare outcomes between the two experimental arms) the study authors concluded that an appropriate ADT intensification regimen for high-risk biochemically relapsed castration-sensitive prostate cancer may be ADT plus apalutamide. It remains to be seen whether delays in PSA progression translate into delays in disease metastasis. Data on secondary outcome measures including metastasis-free survival and overall survival (OS) are immature.

J Clin Oncol. 2024; Jan 23; Online ahead of print



Salvage therapy for prostate cancer: AUA/ASTRO/SUO Guideline

The American Urological Association (AUA), the American Society for Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO) have collectively published guidelines to assist clinicians treating patients with biochemical recurrence of prostate cancer after definitive local treatment of clinically localised disease. This is an additional resource designed to aid in the care of patients not specifically covered in the AUA/ASTRO Localized Prostate Cancer Guideline or the AUA/ASTRO/SUO Salvage Therapy for Prostate Cancer Guidelines, and constitutes a modernisation of the 2013 AUA/ASTRO Adjuvant and Salvage Radiotherapy after Prostatectomy Guideline. Informed by an up-to-date systematic literature review - and necessitated by significant changes in the treatment landscape of this disease state including the introduction of novel imaging modalities and tracers, therapeutic agents and prognostic markers to optimise patient selections - the three-part guidelines supply 30 evidence- and consensus-based statements for the evaluation and management of disease recurrence in three contexts:

- Part 1: treatment decision-making at the time of suspected biochemical recurrence after radical prostatectomy
- Part 2: treatment for non-metastatic biochemical recurrence after primary radical prostatectomy
- Part 3: salvage therapy after radiotherapy and focal therapy, regional recurrence, and oligometastasis

Part I: Introduction and treatment decision-making at the time of suspected biochemical recurrence after radical prostatectomy

A total of 12 guideline statements regarding salvage treatment decision-making at the time of suspected biochemical recurrence after primary radical prostatectomy are provided in this publication. The clinical principle is stated as, "Clinicians should inform patients that salvage radiation after radical prostatectomy poses inherent risks to urinary control, erectile function, and bowel function. These risks must be considered in the context of the risks posed by recurrent cancer along with patient life expectancy, comorbidities, and preferences to facilitate a shared decision-making approach to management".

Strong and moderate recommendations supported by at least evidence level B are as follows:

1. Patients should be informed that salvage radiation for a detectable PSA level after radical prostatectomy is more effective when given at lower levels of PSA
2. Salvage radiotherapy is recommended when the PSA is ≤ 0.5 ng/mL
3. Prognostic factors such as PSA doubling time, Gleason Grade Group, pathologic stage, surgical margin status, validated post-prostatectomy genomic classifier and/or positron emission tomography (PET) imaging results can be used to counsel patients about the risk of clinical progression
4. Next-generation molecular PET imaging should be employed to inform decisions regarding salvage radiotherapy
5. Radiation treatment plans should include therapy to any PET/computed tomography (CT) positive pelvic nodal disease

Conditional recommendations suggest that patients at high risk of clinical progression may undergo salvage radiotherapy at a lower PSA threshold (< 0.2 ng/mL); that evaluation of recurrence may be conducted using prostate-specific membrane antigen (PSMA) PET as an alternative to conventional imaging such as CT, multiparametric MRI (mpMRI) and bone scan with technetium-labelled radiotracers and that pelvic magnetic resonance imaging (MRI) may be added to PET/CT.

Based on expert opinion the guidelines advocate for the use of ultrasensitive PSA assays to enable earlier identification of detectable PSA levels in patients at high risk of recurrence but caution that a rising PSA trend should be observed prior to salvage therapy initiation in patients who do not meet the AUA definition of biochemical recurrence after radical prostatectomy (PSA ≥ 0.2 ng/mL). Expert opinion also states that negative PET/CT imaging results in the context of post-prostatectomy biochemical recurrence should not preclude the receipt of salvage prostate bed radiotherapy.

J Urol. 2024; Feb 19; Online ahead of print

Part II: Treatment delivery for non-metastatic biochemical recurrence after primary radical prostatectomy

Ten guideline statements detail treatment delivery for non-metastatic biochemical recurrence after primary radical prostatectomy. The guiding principle advises that a shared decision-making principle be adhered to in this treatment space with consideration given to potential adverse effects from ADT and salvage radiotherapy in the context of relevant medical comorbidities.

Recommendations are summarised herein:

- At least four to six months of ADT in addition to salvage radiotherapy is indicated in all cases with any high-risk feature and for all patients with pN1 disease. Based on expert opinion it is suggested that ADT may be extended to 24 months
- Conditional recommendations suggest that radiotherapy alone may be utilised in patients without any high-risk clinical and/or pathologic features
- Radiation fields may include the regional lymph nodes with the caveat that patients are informed of the increased risk of short-term side effects
- Docetaxel is not recommended in patients undergoing ADT and salvage radiotherapy
- In the absence of node-positive disease, the use of intensified androgen receptor suppression with salvage radiotherapy should be restricted to clinical trials

J Urol. 2024 Feb 14; Online ahead of print

Part III: Salvage therapy after radiotherapy or focal therapy, pelvic nodal recurrence and oligometastasis, and future directions

Evaluation and management of suspected non-metastatic recurrence after radiation therapy

A prostate biopsy is required to appraise local recurrence in cases of biochemical recurrence without evidence of disease dissemination after primary radical prostatectomy or ablative therapy. A moderate strength recommendation endorses the use of salvage radical prostatectomy, cryoablation, high intensity focused ultrasound, or reirradiation in cases of biopsy-confirmed recurrent prostate cancer.

Evaluation and management of suspected non-metastatic recurrence after focal therapy

Although the absence of clear data to inform the optimal therapeutic approach in this setting precludes evidence-based guidelines, expert consensus opinion from the Salvage Therapy for Prostate Cancer Panel suggests that whole gland treatment via radical prostatectomy or radiotherapy is appropriate.

Evaluation and management of regional recurrence

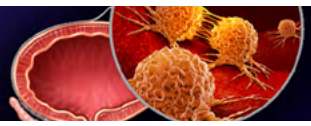
A consensus expert opinion proposes that in the scenario of isolated pelvic nodal recurrence after primary radical prostatectomy or primary radiotherapy without pelvic nodal radiation, salvage comprehensive radiotherapy to the prostate bed and pelvis in combination with ADT offers the greatest likelihood of clinical benefit. Salvage therapy in patients who received prior pelvic lymph node radiotherapy at the time of primary prostate radiotherapy may involve salvage lymphadenectomy, reirradiation with stereotactic ablative radiotherapy or ADT monotherapy, with recognition that very limited data exists in this treatment space. Finally, with the provision that patients are appropriately educated regarding the uncertain oncologic benefit and the risks, salvage pelvic lymphadenectomy may be an option in select patients with recurrent pelvic lymph node disease following primary radical prostatectomy or radiotherapy (Conditional Recommendation).

Management for molecular imaging metastatic recurrence

Reirradiation with stereotactic ablative radiotherapy is conditionally recommended for patients with evidence of regional or metastatic oligorecurrence after definitive primary treatment with the proviso that the toxicity-benefit balance be considered. In the panel's expert opinion, salvage prostate bed radiotherapy may be omitted in cases of biochemical recurrence with non-regional disease detected on PET/CT but not visible on conventional imaging.

This publication is a valuable resource for clinicians managing patients with recurrent prostate cancer following primary definitive treatment.

J Urol. 2024; Feb 14; Online ahead of print



Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study

Data from the retrospective international WARMTH Act study indicate that Actinium-225 (^{225}Ac) PSMA radioligand therapy is an effective later-line therapy in patients with metastatic castration-resistant prostate cancer (mCRPC). Outcomes were analysed in a cohort of 488 patients with pre-treated mCRPC who received at least one cycle of intravenously administered 8 MBq ^{225}Ac-PSMA radioligand therapy (median, 2 cycles) in a roughly seven-year period up to May 2023. The study cohort were heavily pre-treated, with ^{225}Ac-PSMA radioligand therapy predominantly used as a last-line option after failure of all approved agents including taxane-based chemotherapy, androgen-receptor-axis inhibitors, lutetium-177 (^{177}Lu) PSMA radioligand therapy and radium-223 dichloride. Substantial antitumour activity was reported with outcomes at a median nine-month follow-up including a median OS and PFS of 15.5 and 7.9 months, respectively. Superior survival outcomes were found in patients with a PSA decline of ≥ 50%, patients without liver or peritoneal metastases, patients without anaemia and patients with no prior exposure to taxane-based chemotherapy, androgen-axis-receptor inhibitors or ^{177}Lu–PSMA radioligand therapy. The most common adverse event was xerostomia, reported by more than two-thirds of patients after the first treatment cycle and in all patients who received more than seven cycles. Severe adverse events were relatively infrequent and mostly haematological or renal (≥ grade 3 anaemia, 13%; leukopenia, 4%; thrombocytopenia, 7%). There were no serious adverse events or treatment-related deaths.

Lancet Oncol. 2024;25(2):175-83

Plant-based diet associated with better quality of life in prostate cancer survivors

A diet predominantly comprised of plant-based material may be a lifestyle modification that can improve quality of life in men after treatment for localised prostate cancer, with this study reporting benefits in sexual and urinary health associated with greater consumption of plant-based foods. In order to examine correlations between diet indices and quality of life American researchers analysed longitudinal self-reported food-frequency and quality of life data from just over 3,500 men with nonmetastatic prostate cancer participating in the ongoing Health Professionals Follow-Up Study. Most of the study population received radical prostatectomy or radiotherapy as their primary oncology treatment and commenced food- and health-related questionnaires at a median of seven years post diagnosis/treatment. Generalised estimating equation analysis revealed modest improvements in sexual function and urinary health with a higher plant-based diet index after adjustment for confounding factors including demographics, oncologic history, body mass index, caloric intake, health-related behaviours and comorbidities. Comparison of quintiles with diets consisting of the highest and lowest proportion of plant material, respectively, showed improvements of up to 11%-14% in measures of sexual function, urinary health and hormonal/vitality health in the highest quintile, with lower rates of urinary incontinence, obstructions and irritation as well as fatigue/low energy and depression. The authors concluded that the greater consumption of fruits and vegetables with limited intake of meat and animal products may be a simple measure to improve quality of life after primary treatment for early-stage prostate cancer.

Cancer. 2024; Feb 13; Online ahead of print

Long-term results of dose escalation (80 vs 70 Gy) combined with long-term androgen deprivation in high-risk prostate cancers: GETUG-AFU 18 randomized trial

Data from the phase 3 GETUG-AFU 18 trial - presented at the 2024 American Society of Clinical Oncology Genitourinary Cancers Symposium – support escalation of radiotherapy dose in patients with high-risk, clinically node-negative, nonmetastatic prostate cancer receiving long-term ADT, demonstrating benefits in both durable suppression of PSA levels as well as cancer-specific survival and OS. The French trial accrued over 500 men with histologically confirmed adenocarcinoma of the prostate considered high-risk due to high clinical stage, Gleason score or serum PSA level (T3 or T4, ≥8 and ≥20 - ≤100 ng/mL, respectively) without evidence of pelvic or axillary lymph node or bone metastasis. Patients received three-years of ADT plus dose-escalated (80 Gy) or conventional-dose (70 Gy) radiotherapy. Significant improvements in biochemical or clinical PFS with dose-escalated radiotherapy were found, improving rates from 88.1% to 91.4% at five-years and from 79.2% to 88.1% at seven years. Longer follow-up additionally revealed that the reduction in the risk of disease progression is durable, with ten-year biochemical or clinical PFS rates of 83.6% in the dose-escalated radiotherapy arm versus 72.2% in the conventional-dose arm (HR 0.56; p=0.0005). At ten years, significant prostate cancer-specific survival and OS benefits were also reported, with hazard ratios of 0.48 and 0.61, respectively. Incidence of late genitourinary and gastrointestinal toxicities and quality of life were comparable between treatment arms. It was concluded that high-dose radiation therapy with long-term ADT should be the standard of care in high-risk nonmetastatic prostate cancer.

J Clin Oncol 2024; 42 (suppl 4; abstr LBA259)

News in Brief

Interim results from a phase 1/2 study of HPN328, a tri-specific, half-life extended DLL3-targeting T-cell engager, in patients with neuroendocrine prostate cancer and other neuroendocrine neoplasms

Early-phase trial data from an investigational delta-like canonical Notch ligand 3 (DLL3)-targeting T-cell engager - HPN328 - suggests it has activity in neuroendocrine carcinomas, including prostate cancer. Intravenous HPN328 monotherapy was investigated in 14 dose-escalation cohorts ranging from 0.015 to 24 mg, administered weekly or biweekly. In ten patients with neuroendocrine prostate cancer half achieved an unconfirmed partial response.

J Clin Oncol 2024; 42 (suppl 4; abstr 121)

Prostate cancer screening uptake in transgender women

The importance of active advocacy for PSA screening in transgender women by health professionals is highlighted by findings from this US case-control study that suggests that differences in patterns of care may drive the low screening rates. Matched analysis of 255 transgender women and over 1,000 cisgender men revealed that the former were significantly less likely to have undergone recent PSA screening (odds ratio 0.65), with one-fifth of 55- to 69-year-old transgender women versus over one-third of cisgender men undergoing screening in the last two years. This association lost statistical significance on analysis considering whether a clinician recommended a PSA test.

JAMA Netw Open. 2024;7(2):e2356088

Association between change in cardiorespiratory fitness and prostate cancer incidence and mortality in 57 652 Swedish men

This Swedish observational study of over 57 thousand men suggests that improving cardiorespiratory fitness may reduce the risk of developing prostate cancer. Over a roughly seven-year follow-up period 1% of the study population developed prostate cancer with a cancer-specific mortality rate of 0.08%. The study identified a link between improvements in cardiorespiratory fitness and reduced prostate cancer incidence, but not mortality.

Br J Sports Med. 2024; Feb 26; Online ahead of print

2024 MOGA annual scientific meeting

The 2024 Medical Oncology Group of Australia (MOGA) Annual Scientific meeting will be held at the International Convention & Exhibition Centre in Sydney from the 14-16th August.

Registration is now open online here

COVID-19 Resources

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

Conferences, Workshops, and CPD

Please click on the links below for upcoming local and international prostate cancer meetings, workshops and CPD.

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

Research Review Publications

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

Urology Research Review with Professor Eric Chung