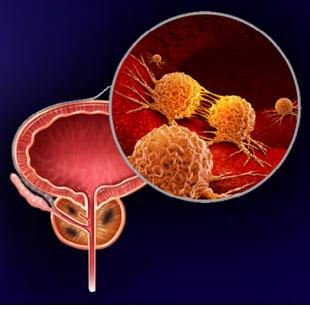
Prostate Cancer Practice Review™



Making Education Easy

Issue 15 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy; **ASCO** = American Society of Clinical Oncology; **BCR** = biochemical recurrence; **CAPRA** = Cancer of the Prostate Risk Assessment; **EBRT** = external-beam radiation therapy; **EPE** = extraprostatic extension; **HDR** = high dose-rate; **HR** = hazard ratio; **mCRPC** = metastatic castrate-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MRI** = magnetic resonance imaging; **OS** = overall survival; **PCSS** = prostate cancer–specific survival; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **SVI** = seminal vesicle invasion.

Welcome to the 15th 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,

Dr Janette Tenne
Editor
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Clinical Practice

Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials

Three large randomised trials - GETUG-AFU 15, CHAARTED and STAMPEDE – investigated whether the addition of early chemotherapy to androgen-deprivation therapy (ADT) conferred a clinical benefit in patients with metastatic hormone-sensitive prostate cancer (mHSPC). Although results were inconsistent, with CHAARTED and STAMPEDE both demonstrating a significant clinically meaningful survival benefit to front-line chemohormonal therapy with crude extensions in overall survival (OS) of up to 12 months over ADT alone, GETUG-AFU reported no improved survival and reduced tolerability with chemotherapy. Synthesis of aggregate evidence in subsequent meta-analyses supported the concomitant use of docetaxel chemotherapy in fit patients initiating hormonal treatment for metastatic disease and this finding was reflected in guidelines. Intensification of ADT with doublet regimens mostly transitioned from docetaxel to androgen receptor signalling inhibitors until the recent discovery that triplet regimens incorporating all three therapies may have the optimal efficacy (ENZAMET trial; *Lancet Oncol* 2023;24[4]:323-34).

In this context, the STOPCAP M1 collaboration conducted a systematic review and meta-analysis of individual participant data from randomised trials to delineate which patients with mHSPC would plausibly derive benefit from docetaxel in addition to ADT-based therapy, and conversely, elucidate patient populations for whom this combination is not ideal. Data on over 22 hundred men with mHSPC who received ADT ± docetaxel in the GETUG-AFU 15, CHAARTED or STAMPEDE trials (median follow-up over six years) were included in random-effects meta-analysis. Overall, doublet therapy including docetaxel was found to outperform ADT alone, eliciting 9% to 11% improvements in absolute five-year OS, progression-free survival (PFS) and failure-free survival rates with hazard ratios (HRs) ranging from 0.64 to 0.79 and little statistical between-trial heterogeneity (p=0.32, I^2=13%). Metastasis volume and clinical T stage were both identified as independent factors modifying the effect of docetaxel. Timing of disease diagnosis – synchronous or metachronous – had a small impact on effect of docetaxel but lost correlation when other interactions were considered. Age, body mass index, WHO performance status, Gleason sum score, risk and clinical N stage had no impact on docetaxel efficacy. Flexible parametric modelling and regression standardisation analyses showed that the benefit conferred by the addition of docetaxel was greatest in patients with high-volume (both high metastatic burden and bulky primary tumour) clinical T stage 4 disease (35% improvement in five-year OS, 20% vs 55%). The study authors were unable to find evidence that docetaxel improved outcomes in patients with low-volume, metachronous disease and recommended that alternative therapeutic options be employed in this population.

Lancet Oncol. 2023;24(7):783-97

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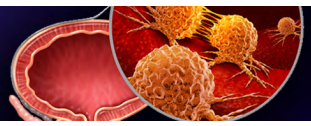

Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update

The American Society of Clinical Oncology (ASCO) have published an update to their 2021 guidelines on the initial management of noncastrate advanced, recurrent or metastatic prostate cancer. The focused update was prompted by clinical trial data demonstrating a survival advantage to triplet regimens incorporating a novel direct androgen receptor inhibitor or an inhibitor of androgen biosynthesis to an ADT plus docetaxel backbone over standard of care alone in de novo noncastrate metastatic disease and their subsequent approval by regulatory bodies.

A multidisciplinary Expert Panel developed the modernised therapeutic recommendations based primarily on data from the ARASENS and PEACE-1 trials regarding the efficacy of darolutamide and abiraterone-based triplet regimens, respectively. Long-term results from ENZAMET and ARCHES for the durability of improved outcomes with the newer anti-androgen enzalutamide versus conventional anti-androgens on a background of ADT ± docetaxel chemotherapy were also provided. In the absence of head-to-head trial evidence to decipher whether docetaxel remains relevant in this era of novel agents achieving profound testosterone suppression, a network meta-analysis weighing up ADT plus an androgen receptor axis–targeted agent, or ADT plus docetaxel informed directions. For noncastrate metastatic prostate cancer a strong evidence-based recommendation suggests that standard of care constitute a doublet of ADT plus either docetaxel, abiraterone, enzalutamide, apalutamide or darolutamide. Front-line triplets of ADT and docetaxel plus either abiraterone or darolutamide are suggested for de novo high-volume metastatic disease only, such as patients with ≥ four bone metastases including at least one outside of the spine or pelvis and/or visceral disease. Cost may be a deciding factor when choosing between darolutamide and abiraterone. In cases of high-volume disease where triplet therapy is not possible due to financial limitations the guidelines advocate for ADT plus docetaxel. Docetaxel chemotherapy use should be restricted to the first-line setting for de novo metastatic disease or high-volume disease per CHAARTED and GETUG-AFU-15 data. The advice to use enzalutamide plus ADT in both the front-line setting for de novo noncastrate metastatic disease and as a second-line therapy in chemotherapy-naïve patients after radical prostatectomy, radiation therapy or ADT remains unchanged from the previous guideline iteration.

J Clin Oncol. 2023;41(20):3652-56

Coffee intake, caffeine metabolism genotype, and survival among men with prostate cancer

Regular coffee drinking has been linked to a lower relative risk of developing a range of malignancies including liver, bowel, breast and prostate cancer. With respect to prostate cancer, an inverse association between coffee intake and risk of development has been reported in multiple studies including a 2017 Italian study published in the *International Journal of Cancer* (Pounis G et al. 2017;141[1]:72-8), a prospective analysis in the US Health Professionals Follow-up Study (Wilson K et al. *J Natl Cancer Inst.* 2011;103[11]:876-84) and more recently, in a meta-analysis of 16 studies including over one million men (Chen X et al. *BMJ Open*; 2021;11[2]:e038902). Although the underlying mechanisms remain unknown, plausible explanations include anti-inflammatory and antioxidant effects and impact on sex hormones.

Now, an analysis of data from the international PRACTICAL Consortium database suggests that a high consumption of coffee may also protect against prostate cancer-specific death after a prostate cancer diagnosis in men with a rapid caffeine metabolising genotype. The study pooled patient-level data from seven studies in the US, Australia and Europe (n=5,727) and utilised multivariable-adjusted Cox proportional hazards modelling to evaluate correlations between low, high or no coffee intake with OS and prostate cancer–specific survival (PCSS). A non-statistically significant trend towards improved PCSS and OS was found with high versus low- or intermediate coffee consumption in the overall cohort (HR 0.85 and HR 0.90, respectively) and in both localised and advanced disease (HR 0.66 and HR 0.92). Analysis stratified by *CYP1A2* –163C>A rs762551 single-nucleotide variants revealed that the PCSS benefit conferred by a high coffee intake was restricted to men with the AA fast caffeine metabolising genotype (HR 0.67; 95% confidence interval 0.49–0.93; p=0.017). No benefit on OS was seen with high coffee consumption in any of the caffeine metabolising genotypes. With the caveat that these findings require confirmation, coffee-based interventions may be a novel adjunct therapy in specific populations with prostate cancer to augment pharmacotherapies.

Eur Urol Oncol. 2023;6(3):282-28

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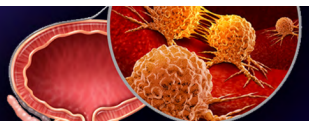
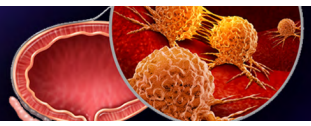




Long-term outcomes of ultra-hypofractionated 2 fractions single day HDR brachytherapy in localized prostate cancer

High dose-rate (HDR) brachytherapy is a safe and effective local treatment modality for favourable non-metastatic prostate cancer that provides durable cancer control, according to long-term results from a Spanish single-centre study. A total of 120 men (median age, 66 years; median prostate-specific antigen [PSA], 7.5 ng/ml; Gleason score 6, 84.2%) with low- or intermediate-risk localised prostate cancer were enrolled into the trial between late 2010 and early 2016 and administered two 13.5 Gy fractions in one day. Almost one-third of the study cohort also received ADT. The high rates of no biochemical evidence of disease and metastasis-free survival reported at a median follow-up of 4.4 years (96% and 98%, respectively; Nagore G et al. *Radiother Oncol*. 2018;127[2]:219-24) were maintained at ten-year follow-up (93.3% and 96.1%). Durable local disease control was achieved in 95.2% of patients and the 10-year OS rate was 86.7%. PSA nadirs of ≤ 0.20 ng/mL portended favourable long-term outcome with high rates of durable biochemical control (no biochemical evidence of disease, 96.9% vs 40%). The authors stated that in this population, two fraction HDR brachytherapy monotherapy is a highly curative radiation technique that results in low PSA levels in most patients.

Radiother Oncol. 2023; Jul 10; Online ahead of print

Impact of Asian race on prognosis in de novo metastatic prostate cancer

In order to corroborate epidemiologic data that suggests a favourable prognosis for men of Asian race diagnosed with de novo metastatic prostate cancer compared to other races, individual patient-level data on survival outcomes in men with newly diagnosed metastatic prostate cancer from three cohort studies were analysed in this study.

Data on almost 30 thousand patients of either Asian or White race with de novo metastatic prostate cancer were sourced from three cohorts – the LATITUDE clinical trial of ADT ± abiraterone, the US Surveillance, Epidemiology, and End Results (SEER) database and the US National Cancer Database. Propensity score-matched analysis considering age, PSA level, Gleason score, ECOG status and socioeconomic status was undertaken on 6,335 patients, 25% of whom were Asian including men from China, Japan and Korea *inter alia*. Kaplan-Meier analyses by racial subgroups found superior survival outcomes in Asian versus White men across all three cohorts, regardless of treatment regimen, with extension in absolute median OS of between nine months to two years. Asian race favourably and independently associated with OS on multivariable Cox proportional hazards analysis with HRs ranging from 0.45 to 0.76.

It was noted that the adverse prostate cancer survival often reported in Black versus White patients can be attributed in part to access to, and appropriateness of, therapy - as evidenced by worse outcomes in real-world datasets but not in randomised clinical trial cohorts. This does not seem to be a factor in the disparity in survival in Asian compared to White patients, with Asian patients consistently demonstrating better survival in subgroups treated with ADT alone, ADT plus abiraterone and in both trial cohorts and regular clinical practice. It would be prudent to ascertain the aetiology of this potential survival benefit conferred by Asian race and examination of genetic factors including aberrations in among hormone-metabolizing enzyme genes, oncogenes and suppressor genes as well as microsatellite instability may be warranted.

J Natl Compr Canc Netw. 2023;21(7):733-41

A prospective trial of apalutamide and abiraterone acetate plus prednisone in Black and White men with metastatic castrate-resistant prostate cancer

An interim analysis from the US phase 2 PANTHER trial of the race-specific efficacy of apalutamide and abiraterone acetate plus prednisone (AAAP) for metastatic castrate-resistant prostate cancer (mCRPC) was presented at the 2023 ASCO Annual Meeting by Dr Daniel George from the Duke Cancer Institute Centre for Prostate and Urologic Cancers in North Carolina. The trial enrolled men with a metastatic adenocarcinoma of the prostate with evidence of castration-resistant disease in the setting of ongoing ADT with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist (unless prior bilateral orchiectomy had been performed) who were naïve to androgen receptor pathway inhibitor therapy in two cohorts – White patients (n=50) and Black patients (n=43). Both cohorts received up to two years of open-label apalutamide, abiraterone acetate and prednisone (240 mg once-daily, 1000 mg once-daily and 5 mg twice-daily, respectively) through the same care teams at the same institutions. The trial reported a differential response to secondary hormonal therapy by race, with Black patients deriving greater benefit than White patients including delays in radiographic PFS (30 vs 15 months), prolonged survival, greater declines in PSA levels and longer time to PSA progression.

The findings are consistent with those from the Abi Race trial where Black patients achieved better and more durable responses to abiraterone acetate plus prednisone than White patients. Follow-up in PANTHER is ongoing with final results expected in 2025.

J Clin Oncol 2023; 41 (suppl 16; Abstract 5015)

Effect of brachytherapy with external beam radiation therapy versus brachytherapy alone for intermediate-risk prostate cancer

The NRG Oncology RTOG 0232 randomised clinical trial, a US phase 3 multicentre study, was conducted to evaluate the hypothesis that combining interstitial brachytherapy with external-beam radiation therapy (EBRT) may be more efficacious than brachytherapy alone for patients with intermediate-risk prostate cancer. Men with an intermediate-risk prostate adenocarcinoma without evidence of distant metastasis (n=579; T1c-T2b, N0, M0; Gleason score < 7 plus PSA 10-20 ng/mL or Gleason score 7 and PSA < 10 ng/mL) were enrolled and randomised to receive transperineal interstitial permanent brachytherapy with 125 Gy Palladium-103 or 145 Gy Iodine-125 seeds ± EBRT to the prostate and seminal vesicles (1.8 Gy five times per week; total dose of 45 Gy). The addition of an external beam radiation boost to brachytherapy did not significantly improve five-year rate of freedom from progression - in analysis where FFP was defined as PSA failure using the American Society for Radiation Oncology (ASTRO) criteria or the Phoenix definition including local failure, distant failure or any-cause death (85.6% vs 82.7% and 88% vs 85.5%, respectively). The combination therapy resulted in higher rates of late genitourinary and gastrointestinal toxicity and the authors concluded that brachytherapy monotherapy should remain the standard for intermediate-risk prostate cancer.

J Clin Oncol. 2023; Jun 14. Online ahead of print

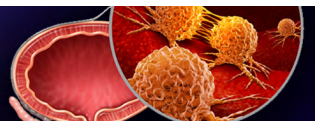
Comparison of MRI-based staging and pathologic staging for predicting biochemical recurrence of prostate cancer after radical prostatectomy

Pre-operative magnetic resonance imaging (MRI)-based diagnostic characteristics may have a comparable accuracy for prediction of post- prostatectomy biochemical recurrence (BCR) as pathologic evaluation of radical prostatectomy specimens in patients with prostate cancer, according to results from this retrospective study.

The study contrasted correlations between extraprostatic extension (EPE) and seminal vesicle invasion (SVI) visualised on pre-surgical MRI or by postoperative pathologic staging and post-surgical BCR in a cohort of 604 patients (median age, 60 years). The presence of either prostate attribute - whether identified pre- or post-prostatectomy - negatively associated with BCR, with Kaplan-Meier estimates of three-year BCR-free survival 25%-31% higher in patients with EPE compared to without EPE (on MRI, 84% vs 59%; prostatectomy pathology, 89% vs 58%; both $p<0.001$) and 29% to 31% higher in patients with SVI compared to those without (MRI, 82% vs 50%; prostatectomy pathology, 83% vs 54%; both $p<0.001$). Cox proportional hazard modelling analysis revealed a 3.5-fold elevated risk of post-operative BCR of prostate cancer with EPE identified on pre-surgical MRI and a five-fold higher risk when found in pathologic staging. Similarly, the risk of BCR associated with pre- or post-operative identification of SVI was approximately five-fold higher compared to patients without this characteristic. Evaluation of two clinical BCR prediction models (University of California San Francisco-Cancer of the Prostate Risk Assessment [CAPRA] and CAPRA-S models) and two CAPRA-MRI models found that only the models considering MRI-visualised factors differentiated low- and medium-risk groups by recurrence-free survival rates and BCR risk.

The authors claim that these findings warrant incorporation of MRI findings into BCR prediction models. Accurate disease staging without reliance on surgical specimens enables earlier therapeutic decision-making including consideration of neoadjuvant therapies and improve outcome prediction in patients undergoing non-surgical treatments or surveillance.

AJR Am J Roentgenol. 2023; Jul 5. Online ahead of print



News in Brief

New pathway for cisplatin prodrug to utilize metabolic substrate preference to overcome cancer intrinsic resistance

Using biopsy samples from 38 patients with prostate cancer this preclinical work from a group at the University of Miami in the US exhibited that Platin-L, a cisplatin-containing prodrug compound, overcomes prostate cancer cell chemotherapy resistance by binding to the mitochondrial protein CPT1A (carnitine palmitoyltransferase 1 A) and blocking fatty acid oxidation. Platin-L was transformed into an oral therapy utilising previously developed nanoparticles and demonstrated preliminary efficacy in murine models of prostate cancer. As well as rendering prostate cancer cells susceptible to cisplatin, this novel therapy may be less hepato- and nephrotoxic than chemotherapy delivered non-orally and may reduce the risk of peripheral neuropathy.

ACS Cent Sci. 2023;9(7):1297-312

Salvage cryoablation for recurrent prostate cancer following primary external beam radiotherapy or primary cryotherapy

A propensity score-matched analysis of mid-term oncologic and functional outcomes reports that salvage cryotherapy for local prostate cancer recurrence is equally as effective after primary cryotherapy as after primary EBRT. The study analysed data from the Duke Prostate Cancer database and the Cryo On-Line Data (COLD) registry. At up to five-years follow-up after salvage cryotherapy no difference in biochemical PFS or functional outcome was found according to primary focal therapy modality.

Clin Genitourin Cancer. 2023; Jun 28. Online ahead of print

Implementation of a telehealth genetic testing station to deliver germline testing for men with prostate cancer

The Helen Diller Family Comprehensive Cancer Centre has implemented a so-called genetic testing station, a collaboration between oncologists and genetic counsellors designed to streamline genetic testing and increase access for men with prostate cancer. In a cohort of 713 men with prostate cancer referred to the station over a two-year period in 2019-2021, most completed germline testing (83%) within two months and at least one pathogenic genetic variant was identified in 13%. Although the model has been adopted by multiple clinics and is a feasible way to offer high-volume genetic testing it did not overcome racial disparities in access.

JCO Oncol Pract. 2023;19(5):e773-83

New prostate cancer patient-centered website

A new educational website ***Prostate Cancer Patient Voices*** has been launched. The platform aims to educate and support patients after a diagnosis by offering a mix of evidence-based resources and patient stories, with a focus on linking individuals with other men at the same place in their treatment journey. The website was established by the Prostate Cancer Foundation in collaboration with UroToday and has sponsorship from Bayer Pharmaceuticals.

The website can be found here

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