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Abbreviations used in this issue:

ADT = androgen deprivation therapy; ARIR = adjusted HR; CI = confidence interval; HR = hazard ratio; mpMRI = multiparametric magnetic resonance imaging; NCNN = National Comprehensive Cancer Network; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA-PE/TCT = prostate-specific membrane antigen positron-emission tomography/computed tomography; SEER = Surveillance, Epidemiology, and End Results.

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Welcome to issue 24 of Prostate Cancer Research Review.

The pre-diagnostic use of 5α-reductase inhibitors is associated with delayed diagnosis and worse cancer-specific outcomes in men with prostate cancer, according to the findings of a recent study published in JAMA Internal Medicine. The study highlights a continued need to raise awareness of 5α-reductase inhibitor-induced PSA suppression and to establish clear guidelines for the detection of prostate cancer in users of 5α-reductase inhibitors. Other topics covered in this issue include alcohol intake and risk of lethal prostate cancer, active surveillance in intermediate-risk prostate cancer, robot-assisted radical prostatectomy after focal therapy, physical activity and prostate cancer, and cardiovascular risk knowledge in prostate cancer patients.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

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Detection and localisation of primary prostate cancer using 68Ga-PSMA PET/CT compared with mpMRI and radical prostatectomy specimens

Authors: Kalapara AA et al.

Summary: This multicentre retrospective (2015-18) review compared 68Gallium-PSMA PET/CT with multiparametric (mp)MRI for detection and localisation of primary prostate cancer compared with radical prostatectomy pathology of 205 men. 68Ga-PSMA PET/CT and mpMRI did not differ in the detection of any tumour (94% vs 95%) and there was no difference between localisation of all index tumours (91% vs 89%), clinically significant index tumours (96% vs 91%), or transition zone tumours (85% vs 80%).

Comment: The PRIMARY trial, which is just opening in Australia, will serve to examine prospectively a limited PSMA versus standard community MRI and it will be interesting if there is a difference. On another note, good to see a local study making inroads into the PSMA research space again (even if I am a co-author I might say). This type of collaborative research is important in our region to get the numbers up and punch higher and harder on the world stage.

Reference: BJU Int. 2019; Jul 1 [Epub ahead of print]

Association of treatment with 5α-reductase inhibitors with time to diagnosis and mortality in prostate cancer

Authors: Sarkar RR et al.

Summary: This US population-based cohort study used Veterans Affairs data and the National Death Index to link data for 80,875 men (median age at diagnosis 66 years) with stage I-IV prostate cancer (2001-15) to assess pre-diagnostic 5α-reductase inhibitor (5-ARI) use and its association with delayed diagnosis, more advanced disease stage at diagnosis, prostate cancer-specific mortality and all-cause mortality versus other non-PSA-decreasing drugs. Over a median follow-up of 5.9 years, the median time from first adjusted elevated PSA to diagnosis was greater in those receiving 5-ARIs (3.60; 95% CI 1.79-6.09 years) versus nonusers (1.40; 95% CI 0.38-3.27 years; p < 0.001) in those with a known prostate biopsy date. Median adjusted PSA at biopsy was also higher (13.5 vs 6.4 ng/mL; p < 0.001) in 5-ARI recipients who were also more likely to have disease that was Gleason grade ≥8 (25.2% vs 17.0%; p < 0.001), clinical stage T3 or higher (4.7% vs 2.9%; p < 0.001), node-positive (3.0% vs 1.7%; p < 0.001) and metastatic (6.7% vs 2.9%; p < 0.001). Multivariate regression indicated that patients who received 5-ARIs had higher all-cause (HR 1.10; 95% CI 1.05-1.15; p < 0.001) and prostate cancer-specific (sub-distribution HR 1.39; 95% CI 1.27-1.52; p < 0.001) mortality.

Comment: This is a concerning paper as we already know that PSA kinetics are poorly managed at times when men are placed on 5-ARIs for benign prostatic hyperplasia. Indeed, often men have no PSA tests done, which is of concern as we do not know if the expected drop in PSA occurs. Also when PSA is done, many men (and often their GP) mistakenly believe the drug is ‘treating their PSA’. On face value it is, but it is not diminishing the risk of prostate cancer. Then it is the rise that is subsequently misclassified, readings taken literally instead of doubting and forgetting to double the new baseline. Legal actions have already arisen for PSA mismanagement in this setting, but that aside, are we doing the right thing by our patients? Moreover the message from this paper is that we need to be more vigilant. Is it time for an MRI in men before we place them on 5-ARIs? Of course this raises the question, for those not qualifying for a funded MRI, who will (or should) pay for it?

Reference: JAMA Intern Med. 2019; May 6 [Epub ahead of print]


### Alcohol intake and risk of lethal prostate cancer in the Health Professionals Follow-Up Study

**Authors:** Downer MK et al.

**Summary:** This prospective cohort study used data on 47,568 cancer-free men and 5182 men with non-metastatic prostate cancer from the Health Professionals Follow-Up Study (1986-2012) to determine whether alcohol intake was associated with a diagnosis of lethal prostate cancer. Alcohol use resulted in a lower risk of lethal prostate cancer (any vs none HR 0.84; 95% CI 0.71-0.99) with no dose-response relationship. In men with prostate cancer, total alcohol intake was not associated with progression to lethal prostate cancer (any vs none HR 0.99; 95% CI 0.57-1.72), but moderate red wine intake lowered risk (any vs none HR 0.50; 95% CI 0.29-0.86; \( p_{	ext{HR}} = 0.008 \)). Use of 15 to 20 g/day of alcohol after diagnosis was associated with a lower risk of death (HR 0.71; 95% CI 0.50-1.00) than no alcohol intake, and red wine also lowered risk (any vs none HR 0.74; 95% CI 0.57-0.97). The real message here is not just for prevention of lethal prostate cancer, but the ability of low alcohol intake to lower the risk of progression to lethal prostate cancer once it has been diagnosed. Time for sponsorship at our meetings from the wine industry?

**Comment:** Finally drinking alcohol for doctors appears beneficial. . in this case protective against lethal prostate cancer, as long as it’s red wine! Doctors can now practice what they preach (if they haven’t been already). However, the real message here is not just for prevention of lethal prostate cancer, but the ability of low alcohol intake to lower the risk of progression to lethal prostate cancer once it has been diagnosed. Time for sponsorship at our meetings from the wine industry?

**Reference:** J Clin Oncol. 2019;37(17):1499-11

### Use and early mortality outcomes of active surveillance in patients with intermediate-risk prostate cancer

**Authors:** Butler SS et al.

**Summary:** This US analysis of data from the SEER Active Surveillance/Watchful Waiting database (2010-15) characterised active surveillance and mortality outcomes in 52,940 actively managed (active surveillance, radiotherapy, or radical prostatectomy) men with NCCN intermediate-risk prostate cancer (cT2b-c, Gleason score 7, or PSA level 10-20 ng/mL). Active surveillance rate almost doubled between 2010 (3.7%) and 2015 (7.3%) and increased from 7.2% to 11.7% in men aged ≥70 years. Active surveillance also increased in those with favourable (7.2% to 14.9%) and unfavourable intermediate-risk disease (2.2% to 3.8%; all \( p_{	ext{HR}} < 0.001 \)). Factors associated with active surveillance included favourable disease risk, black race, higher socioeconomic status, older age, and residence in the West, Northwest or Midwest. The 5-year prostate cancer specific mortality (PCSM) rate did not differ between active surveillance and treatment in those with low-risk and favourable intermediate-risk disease, but was worse in those with intermediate-risk disease overall (1.1% vs 0.4%; aHR 2.34; 95% CI 1.25-4.37; \( p = 0.008 \)) and those with unfavourable intermediate-risk disease (1.3% vs 0.5%; aHR 2.48; 95% CI 1.11-5.50; \( p = 0.026 \)).

**Comment:** We all know exercise is good, but perhaps we really should be prescribing it in the form of exercise physiologist and other allied health visits rather than just mentioning it in passing. Why? Because it works by reducing prostate cancer effects. So, bring on the personal trainers and gym gear, maybe we can convince any non-physical partners too, which would be a double win.


### A prospective study of the association between physical activity and risk of prostate cancer defined by clinical features and \( \text{TMPRSS2:ERG} \)

**Authors:** Pernar CH et al.

**Summary:** This study prospectively collected data (49,160 men aged 40-75 years) from the Health Professionals Follow-Up Study (1986-2012) to examine associations between physical activity and prostate cancer risk defined by clinical features and the transmembrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog (\( \text{TMPRSS2:ERG} \)). Over a total of 26 years of follow-up, 6,411 men developed prostate cancer and 888 men died. There were no associations between total physical activity and risk of prostate cancer, but in multivariate-adjusted models, those in the highest quintile of vigorous activity had a 30% lower risk of advanced prostate cancer (HR 0.70; 95% CI 0.53-0.92) and a 25% lower risk of lethal prostate cancer (HR 0.75; 95% CI 0.50-0.99) than those in the lowest quintile. Vigorous activity was not associated with total prostate cancer overall, but was inversely associated among highly screened men (top vs bottom quintile HR 0.83; 95% CI 0.70-0.97). 945 cases were assayed for \( \text{TMPRSS2:ERG} \) with 48% being ERG-positive. Men with greater vigorous activity levels had a lower risk of ERG-positive prostate cancer (top vs bottom quintile HR 0.71; 95% CI 0.52-0.97).

**Comment:** Extensively interesting as focal therapy becomes more popular; will it make those who fail worse outcomes from surgery? And the answer appears to be, functional outcomes OK, but oncological outcomes sometimes compromised. This was at least partially in the MRI era and not PSMA PET/CT so would we have better tools now to predict recurrence? Are men getting routine post-focal therapy biopsies? All good questions as we grapple with case selection for such treatments.


### Robot-assisted radical prostatectomy after focal therapy: Oncological, functional outcomes and predictors of recurrence

**Authors:** Marconci L et al.

**Summary:** In a multicentre cohort study of 82 patients, researchers characterised outcomes after salvage robot-assisted radical prostatectomy (S-RALP) after local recurrence of prostate cancer following focal therapy and examined risk factors for S-RALP failure. Progression-free survival rates were 71% after 12 months, 48% after 24 months and 36% after 36 months; the 12-month continent rate was 83%. Multivariate analysis suggested that the only independent predictors of recurrence were infelid recurrence (HR 3.77; 95% CI 1.11-12.85; \( p = 0.03 \)) and pT3b stage (HR 5.0; 95% CI 1.53-16.39; \( p = 0.008 \)).

**Comment:** Extremely interesting as focal therapy becomes more popular; will it make those who fail worse outcomes from surgery? And the answer appears to be, functional outcomes OK, but oncological outcomes sometimes compromised. This was at least partially in the MRI era and not PSMA PET/CT so would we have better tools now to predict recurrence? Are men getting routine post-focal therapy biopsies? All good questions as we grapple with case selection for such treatments.

**Reference:** Eur Urol. 2019;76(1):43-51

### A 16-yr follow-up of the European Randomized study of Screening for Prostate Cancer

**Authors:** Hugosson J et al.

**Summary:** The European Randomized study of Screening for Prostate Cancer (ERSPC) multicentre, population-based, randomised screening trial examined whether PSA screening decreased prostate cancer mortality in 182,160 men and assessed results following adjustment for non-participation and the number of screening rounds. Over a maximum follow-up of 16 years, the rate ratio (RR) of prostate cancer mortality was 0.80 (95% CI 0.72-0.89; \( p < 0.001 \)). The number of men screened to prevent one prostate cancer death was 570 at 16 years versus 742 at 13 years and the number needed to diagnose was reduced from 26 at 13 years to 18 at 16 years. Those with prostate cancer detected during first round screening had a higher prevalence of PSA >20 ng/mL (9.9% vs 4.1% in the second round, \( p < 0.001 \)) and higher mortality (HR 1.86; \( p < 0.001 \)) than those detected later.

**Comment:** Remember this trial? ERSPC? Yes, they still do follow the men, and it seems to get more interesting at each cut. Imagine if MRI was available at the start of the trial, where could we be? The number needed to treat still disappointingly does not account for those going on to active surveillance. It would be good to have number needed to have radical treatment as a measure, but unlikely to happen. Still the numbers keep failing and may yet shape our future.

**Reference:** Eur Urol. 2019;76(1):43-51
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Transperineal prostate biopsies using local anesthesia: Experience with 1,287 patients. Prostate cancer detection rate, complications and patient tolerability

Authors: Stefanova V et al.

Summary: This retrospective analysis reviewed 1287 consecutive cases in patients at risk for prostate cancer undergoing transperineal prostate biopsy under local anesthesia. Cancer detection rate was 49.8% with clinically significant prostate cancer in 385 patients and 62 with exclusively anterior zone pathology. Urinary retention requiring temporary catheterisation occurred in 20 (1.6%) patients. One hospital admission occurred for persistent hypotension after biopsy. Most patients tolerated transperineal prostate biopsy reasonably well and most reported only mild levels of discomfort. Anaesthetic infiltration was rated more painful than biopsy.

Comment: Finally, North America is waking and not surprisingly Canada is leading the charge – this time for transperineal biopsy under local anaesthetic. Of course the desire to pursue transperineal biopsy in this manner is derived from the rare resource we take for granted, operating theatre time. We have in abundance, they not. Perhaps it will be embraced and the benefits will flow to all patients, not just here and in the UK.

Reference: J Urol. 2019;201(6):1127-33

New study suggests patients with advanced prostate cancer on androgen deprivation therapy need more dialogue with health care provider, especially around cardiovascular risk

Authors: Merseburger A et al.

Summary: A 10-min online survey of 411 patients was used to assess patients’ awareness, and patient-health care provider dialogue about advanced prostate cancer treatment-related risks, especially cardiovascular (CV) risk. A high CV risk was identified in 83% of respondents, but only 8% were aware of CV risk associated with prostate cancer treatment, the majority of whom were informed by health care providers. Regardless of a patient’s CV risk, no differences in treatment approach were reported. Patients were more likely to initiate discussion about heart problems with health care providers (38%) versus other potential risks. Lifestyle modifications were made by 64% of patients, with 45% reporting improvements in overall wellbeing; dietary change was the most common lifestyle modification.

Comment: Another case for a men’s endocrine clinic or at least better guidelines for GPs and of course urologists and other specialists treating men with ADT. The side effects of treatment are well established and we seem to ignore them at our patient’s expense. We must do better. Comprehensive programs such as True North can assist and we should refer if our services are not immediately available.


Long-term implications of a positive post-treatment biopsy in patients treated with external beam radiotherapy for clinically localized prostate cancer

Authors: Zelefsky MJ et al.

Summary: This study examined the prognostic relevance of post-treatment biopsy after prostate radiotherapy in 82 patients with clinically localised prostate cancer. Over a median follow-up of 9 years, positive biopsy (prostatic adenocarcinoma without radiation-induced changes) prevalence was 30%, adenocarcinoma with a severe treatment effect was 22% and negative biopsy was 48%. ADT omission was associated with a 2.6-fold increase in the odds of positive post-treatment biopsy and high-risk disease had a 1.8-fold increase. The 15-year PSA relapse rate associated with negative biopsies was 34%, the rate with severe treatment effect was 36% and with positive post-treatment biopsies was 79% (p < 0.001). The risk of a distant metastasis was 2.6-fold higher in those with a positive biopsy (p < 0.001) after controlling for known predictors, and cause-specific mortality was 2-fold higher with a positive biopsy versus negative or severe-treatment effect biopsy outcomes (HR 2.00; p = 0.022).

Comment: Startling and sobering post-radiation data, a third of men harbour active prostate cancer with another group having treatment effect, making more than half not having clear biopsies. At risk groups have over a 30% chance of PSA relapse at 15 years. Should we be routinely sampling men without biopsy or would imaging with PSMA be less invasive and more useful? Some thought needs to be applied here, and again in Australia we could lead the way.

Reference: J Urol. 2019;201(6):1127-33