Re: Association of Treatment with 5α-Reductase inhibitors with Time to Diagnosis and Mortality in Prostate Cancer

Sarkar RR, Parsons JK, Bryant AK, et al

JAMA Intern Med 2019;179:812–9

Expert's summary:
In this population-based cohort study of 80 875 patients with prostate cancer from the Veterans Affairs Health Care System, 8587 (10.6%) were taking 5α-reductase inhibitors (5-ARIs) at the time of diagnosis [1]. Compared to non-users, 5α-ARI users had longer delays from first elevated prostate-specific antigen (PSA; corrected for the effect of the drug) to prostate biopsy, presented with more high-grade, lymph node–positive metastatic disease, and had worse prostate cancer–specific and all-cause mortality. 5-ARI use was associated with delayed prostate cancer diagnosis and greater mortality among men who underwent PSA screening.

Expert's comments:
We are told that 5-ARIs prevent prostate cancer and do not increase the risk of high-grade disease [2]. If this were true, why did the men in this study who were treated with 5-ARIs develop high-grade, lethal disease? Sadly, this is because we have not been told the full truth. There is no 5α-reductase enzyme in normal or malignant prostatic epithelial cells; it is located in the stroma. Because higher-grade cancers (Gleason >6) have little stroma, 5-ARIs have no effect in reducing Gleason 7–10 disease. 5-ARI treatment reduces the production of PSA by the stroma in benign prostatic hyperplasia. To correct for this effect, men treated with a 5-ARI must multiply their level by 2.0 for the first 2 yr, by 2.3 for years 2–7, and by 2.5 after year 7 [3]. If patients do not know this, they will not realize they may need a biopsy and might miss the opportunity of being diagnosed with curable disease. This explains the findings in this study.

In the original publication from the Prostate Cancer Prevention Trial, which was a randomized, placebo-controlled trial evaluating finasteride for the prevention of prostate cancer, the authors reported a 25% reduction in prostate cancer prevalence and a 68% increase in high-grade disease [2]. Although the authors have argued that the increase in high-grade disease was an artifact, in 2011 the US Food and Drug Administration reported on their independent reanalysis of the study and found that the original published article was severely flawed [4]. They concluded that in the clinical setting, if 150–200 men were treated with a 5-ARI, there would be a reduction in only three to four Gleason 6 cancers, no reduction in Gleason 7, and an increase in one new case of Gleason 8–10 disease. Sarkar et al [1] suggest that their results "include the possibility that 5-ARIs inherently increase the risk of high-grade cancer".

When I first prescribe 5-ARIs, I explain to patients the importance of having their PSA measured regularly for as long as they are taking the drug. I tell them why they need to know those numbers and if their PSA ever increases they need a biopsy. In patients taking a 5-ARI, PSA levels should continue to go down for as long as they are taking them. If their PSA ever goes up at all, the risk of cancer is increased by a factor of three and the risk of high-grade disease by a factor of six [5]. Urologists need to know the full truth about drugs that have lethal potential.

Conflicts of interest: The author has nothing to disclose.

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Patrick C. Walsh*
James Buchanan Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA

*James Buchanan Urological Institute, Johns Hopkins Hospital Park 224, 600 North Wolfe Street, Baltimore, MD 21287, USA.
E-mail address: pwalsh@jhmi.edu.

https://doi.org/10.1016/j.eururo.2019.07.022
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Re: Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging

Johnson DC, Raman SS, Mirak SA, et al

Eur Urol 2019;75:712–20

Experts' summary:
The authors performed a retrospective analysis of 588 patients with 1213 pathologically confirmed tumour foci, with lesion-specific results from multi-parametric magnetic resonance imaging (mpMRI) co-registered with whole-mount pathology (WMP) prostatectomy specimens. The primary objective was to determine the per-lesion detection rate for prostate cancer (CaP) foci by mpMRI.

mpMRI demonstrated sensitivity of 45% for all CaP, and 65% for clinically significant CaP (csCaP). Multifocality was associated with a higher risk of missing CaP foci, with at least one csCaP focus missed by mpMRI in almost 50% of patients.

Experts' comments:
The importance of mpMRI in CaP detection is well recognised. The European Association of Urology (EAU) guidelines for CaP in 2019 cite strong evidence demonstrating the excellent sensitivity of mpMRI for csCaP detection, and hence recommend mpMRI before biopsy in all patients [1].

The study by Johnson et al used radical prostatectomy (RP) as the reference standard for mpMRI accuracy. While WMP provides a gold standard for assessing multifocality and per-lesion detection rates, this is a highly selective csCaP cohort for which specificity and true negative rates for mpMRI cannot be assessed. While mpMRI missed at least one csCaP focus in 34% of this cohort, the number of these men for whom mpMRI already detected another csCaP focus (larger index lesion) was not described.

The PROMIS and PRECISION trials demonstrated that targeted and systematic biopsies when performed alone have similar detection rates for csCaP, but when combined show improved sensitivity [2,3]. Thus, the issue of mpMRI missing smaller nonindex csCaP lesions while accurately detecting the larger index lesions seems a moot point, particularly if the treatment is RP. Furthermore, a well-performed systematic biopsy is likely to detect the smaller missed lesions, but this is not likely to change management.

The use of per-lesion analysis may be more clinically relevant when considering index lesion concordance. We recently assessed this in a series of 235 RP specimens, with concordance reported as 75% [4]. Given that Johnson et al reported smaller size, nonindex status, and multifocality as predictors for missed csCaP, it would be interesting to use per-patient index lesion concordance as a surrogate for mpMRI accuracy in their cohort.

mpMRI has certainly become established as a standard of care before biopsy. With more accurate detection of csCaP potentially altering the RP cohort, it is possible that a future similar retrospective series would reveal better per-lesion mpMRI sensitivity.

***Conflicts of interest*:** The authors have nothing to disclose.

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Samantha G. Koschel[a,b,*], Lih-Ming Wong[a,b], Stefan Heinze[c], Homayoun Zargar[b,d]
[a]*Department of Urology, St. Vincent's Hospital, Melbourne, Australia*
[b]*Department of Surgery, University of Melbourne, Melbourne, Australia*
[c]*Department of Medical Imaging, Royal Melbourne Hospital, Melbourne, Australia*
[d]*Department of Urology, Royal Melbourne Hospital, Melbourne, Australia*

*Corresponding author. St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia.
E-mail address: sgkoschel@gmail.com (S.G. Koschel).

https://doi.org/10.1016/j.eururo.2019.05.020
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Re: Addition of Radium-223 to Abiraterone Acetate and Prednisone or Prednisolone in Patients with Castration-resistant Prostate Cancer and Bone Metastases (ERA 223): A Randomised, Double-blind, Placebo-controlled, Phase 3 Trial

Smith M, Parker C, Saad F, et al

Lancet Oncol 2019;20:408–19

Expert's summary:
In the ERA-223 trial [1] abiraterone (ABI) and radium-223 were combined in a comparison in which men with up to mildly symptomatic, chemotherapy-naïve bone-metastasized castration-resistant prostate cancer were randomised to ABI with or without up to six doses of radium-223 radionuclide treatment. The primary endpoint was symptomatic skeletal event–free survival. Over a period of 29 mo, 806 men were randomly assigned to the groups. A symptomatic skeletal event was defined as use of external beam radiotherapy to relieve skeletal symptoms, a new symptomatic pathological bone fracture, spinal cord compression, or a tumour-related orthopaedic surgical intervention. Fractures of any grade occurred in 112 of 392 patients (29%) in the radium-223 group and 45 of 394 patients (11%) in the placebo group and the study was therefore stopped prematurely. A nonsignificant trend for lower overall survival (OS) was noted in the intervention arm. Spinal cord compression was more frequent among patients not treated with radium-223. Interestingly, most fractures were not at sites of bone metastases in both treatment groups and osteoporotic fractures mainly in the radium-223 arm. Bone fractures were more common in men not taking bone-protecting agents.

Expert's comments:
Recent data on early combination therapies for metastasized prostate cancer could lead one to think that "more is better". Addition of docetaxel to androgen deprivation therapy improved survival for certain patients (CHAARTED, STAMPEDE) [2], as did local radiotherapy to the prostate [3] and ABI in high-risk primary M1 disease. Earlier data from the ALSYMPCA trial in men with castration-resistant disease