

**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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**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

showed that radium-223 was the first radionuclide to improve OS and quality of life in a phase 3 randomised comparison with placebo [4]. The combination of radium-223 with enzalutamide or ABI was considered to be safe, with 21% of patients who received radium-223 discontinuing it because of toxicity [5], a slightly higher rate than the 16% observed in the ALSYMPCA trial without addition of enzalutamide or ABI [4]. In the prospective, nonrandomised, open-label, single-arm, phase 3b study, enzalutamide or ABI combined with radium-223 may have resulted in better outcomes compared to radium-223 monotherapy, although median OS for the combination group was not reached in the initial report, precluding estimation of the statistical significance [5]. The ERA-223 trial showed no survival benefit for the combination of radium-223, prednisone, and ABI, and a higher risk of fractures. On July 26, 2018, the European Medicines Agency issued a warning on the use of radium-223 dichloride in combination with ABI acetate for men with metastasized prostate cancer considering the higher risk of bone fractures and death ([www.ema.europa.eu/en/medicines/human/referrals/xofigo](http://www.ema.europa.eu/en/medicines/human/referrals/xofigo)). It was suggested that use of prednisone may have increased the risk of fractures when combined with radium-223 [6], and combining radium-223 with enzalutamide may still be valid provided it is taken with bone-protecting agents. It remains remarkable, however, that OS is not improved in the radium-223 arm as it was in the ALSYMPCA trial. Looking at differences in population between ALSYMPCA and ERA-223, median OS was 11.3 mo for the control group in ALSYMPCA and approximately 33.3 mo in ERA-223. This may reflect the higher metastatic load in ALSYMPCA versus ERA-223 (>20 metastases in 30% vs 17%), as well as poorer performance status (25% vs 69% Eastern Cooperative oncology Group score 0) and higher frequency of prior docetaxel use (57% vs 1%). This may imply that radium-223 is of more benefit in the management of later-stage disease, preferably in men with sufficient bone protection without ABI use.

**Conflicts of interest:** The author has nothing to disclose.

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## Re: Tea's Value as a Cancer Therapy is Steeped in Uncertainty

Eisenstein M

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### Experts' summary:

Eisenstein reviews the controversial evidence accumulated over the years on the role of green tea and its constituent molecules as potential anticancer weapons for different types of tumor, including prostate cancer (PC). Epidemiological investigations indicate that the frequency of PC is much lower in eastern countries [1] such as China and Japan, where green tea is widely consumed. Specific large-scale studies also point in the same direction, underlining the beneficial effects of green tea in reducing not only the overall risk of cancer mortality [2] but also cardiovascular diseases [3]. Beneficial effects of green tea have largely been ascribed to a family of polyphenolic molecules known as catechins,

mostly epigallocatechin-3-gallate (EGCG), which comprises up to 65% of the total green tea catechin content. However, while EGCG has strong pharmacological effects both in vitro and in in vivo animal models, its therapeutic benefits in humans remain elusive. Several reasons might account for this, the first probably being that the effective dose given to mice would be impractical for use in humans. However, the author also underlines the intriguing outcome of a small-scale Italian study that demonstrated that green tea extracts were effective in preventing high-grade prostate intraepithelial neoplasia from developing into PC [4].

### Experts' comments:

The lack of translation of preclinical green tea studies into successful clinical trials is certainly disappointing and underlines the intrinsic difficulties in studying the medical benefits of natural products in humans. However, there are still several avenues of research that could possibly be exploited. For instance, recent studies have confirmed the