

**Experts' comments:**

Although sparing of neurovascular bundles should intuitively be associated with better EF and continence recovery rates, it is still not clear which part of the NS procedure plays a crucial role and to what extent [2]. This uncertainty constitutes an important rationale for the analysis performed by Capogrosso et al. [1]. The functional outcomes of NS achieved after 10-yr experience are at first disturbingly poor. Recovery rates not only have not improved over the analyzed period, but also have decreased significantly ( $p = 0.01$ ). A possible explanation of this phenomenon lies in a multivariable analysis—after accounting for the stabilization of the clinical and pathological covariate declining trend. Baseline factors have repeatedly been stressed as crucial for functional outcome—recently also of robot-assisted RP (RARP) [3]. It is however obvious that an absolute lack of change in recovery rates is unexpected given the surgical technique refinements and postoperative care improvements. Since functional benefits of RARP are already supported by a small meta-analysis, increasing use of this approach is to be at least signaled [4]. Results of Capogrosso et al. [1] correspond with the aforementioned systematic review—a multivariate analysis revealing the advantage of RARP. Therefore, if adjustment for positive and negative predictors of EF recovery brings no changes, what is the cause of stagnancy?

The recent understanding of NS includes awareness of nerve structures extending into the entire circumference of the periprostatic fascia, and not only neurovascular bundles. Since the high anterior release technique is not always feasible, “preserveness” of NS can be categorized using a dedicated score [5]. Reliable data regarding the extent of sparing cannot be collected retrospectively. It should also be assumed that each surgeon has his or her own “sparing score.” Moreover, despite the exclusion of surgeons who performed <100 procedures, there might have been some who started to operate with a new surgical approach after gaining certain experience with another. Experience is thus not the only confounder. Although the use of phosphodiesterase type 5 seems not to be an issue, more extensive use of other erectile

aids could be missed or unrecorded. Finally, the complex etiology of erectile dysfunction warrants that prevalence of post-RP erectile dysfunction can be in synergy with raising rates of depression. The conclusion that the authors arrived at is therefore fully justified—there is much to be done.

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

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**Re: Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): A Randomised Controlled Phase 3 Trial**

Parker CC, James ND, Brawley CD, et al

*Lancet* 2018;392:2353–66

**Experts' summary:**

In this randomised trial, Parker et al. [1] studied the effect of radiotherapy to the prostate on overall survival (OS) in 2061 men with metastatic prostate cancer (PCa), of whom 1029 were randomised to standard of care (SOC; androgen deprivation therapy [ADT] ± docetaxel) and 1032 were randomised to SOC plus prostate radiotherapy between 2013 and 2016. In unselected newly diagnosed metastatic patients, radiotherapy to the prostate did not improve OS (0.92, 0.80–1.06;  $p = 0.266$ ). In the prespecified subgroup

analysis by baseline metastatic burden (a high metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both), OS was improved in patients with a low metastatic burden who were randomised to radiotherapy (hazard ratio 0.68, 95% confidence interval 0.52–0.90;  $p = 0.007$ ). The authors conclude that prostate radiotherapy should be a standard treatment option for men with a low metastatic burden.

**Experts' comments:**

Several retrospective analyses have noted a survival benefit in men with metastatic PCa who underwent local treatment [2], while a few were not able to confirm these findings [3,4].

Recently, Boeve et al. [5] published data from the HORRAD trial, which randomised 432 patients with

metastatic PCa to ADT with or without prostate radiotherapy between 2004 and 2014. The majority of patients (67%) had more than five bone metastases, and the median prostate-specific antigen level was 142 ng/ml. After a median follow-up of 47 mo, no significant difference was found in OS.

The present study by the STAMPEDE investigators represents the first randomised trial showing a benefit of radiotherapy to the prostate in metastatic PCa patients with a low metastatic burden [1]. The optimal definition of a low metastatic burden is still unclear and needs to be refined further, especially given the evolving landscape of more sensitive imaging tools such as prostate specific membrane antigen positron emission tomography. The current definition of a metastatic burden is based on conventional imaging.

As acknowledged by the authors, several other questions remain unanswered, which include the optimum radiotherapy dose schedule, the role of additional metastasis-directed therapy in this setting, and the value of abiraterone in men receiving radiotherapy. Furthermore, it is unknown whether the results of this trial can be extrapolated to radical prostatectomy in metastatic PCa. While it seems plausible given the hypothesis that an intact primary tumour may continue to shed metastasis, there may be radiation-specific mechanisms such as immunomodulation or an interplay between radiation and androgen deprivation, which contribute to the observed survival benefit by radiotherapy. Results from randomised studies currently underway are needed to answer this question.

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

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## Re: [<sup>177</sup>Lu]-PSMA-617 Radionuclide Treatment in Patients with Metastatic Castration-resistant Prostate Cancer (LuPSMA Trial): A Single-centre, Single-arm, Phase 2 Study

Hofman MS, Violet J, Hicks RJ, et al

*Lancet Oncol* 2018;19:825–33

### Experts' summary:

The authors report on the first prospective, single-arm, phase 2 trial exploring the role of [<sup>177</sup>Lu]-prostate-specific membrane antigen (PSMA)-617 in heavily pretreated patients with metastatic castration-resistant prostate cancer (CRPC) [1]. This is a highly personalized approach using PSMA positron emission tomography (PET)/computed tomography (CT) for noninvasive imaging and quantitation of PSMA expression to select patients most likely to benefit from treatment. This trial provides proof of concept that [<sup>177</sup>Lu]-PSMA-617 has promising antitumour activity, low toxicity, and improves quality of life in CRPC patients.

### Experts' comments:

PSMA is a transmembrane protein expressed in aggressive variants of localized PC and is further upregulated in metastatic and CRPC [2]. Several PSMA PET/CT radiotracers have been developed and are rapidly replacing conventional imaging in settings such as biochemically recurrent PC [3]. In addition to its potential as a diagnostic tool, PSMA is also suitable as a theranostic agent for attachment to radioactive molecules for targeted delivery of radiation to PSMA-positive tumor sites. In the current study, such a targeted approach was applied by selecting [<sup>68</sup>Ga]-PSMA positive patients and excluding patients with [<sup>18</sup>F]-fluorodeoxyglucose-positive PSMA-negative lesions [1].

The results presented by Hoffman and colleagues are promising, with 57% of the patients experiencing a prostate-specific antigen decline of >50% (primary outcome), especially when taking into account that >80% patients had received previous chemotherapy and/or second-line novel anti-androgens [1]. In 14 out of 17 patients with eligible lesions according to RECIST criteria, an objective