

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



European Association of Urology



Platinum Opinion

Treatment of the Primary Tumor in Metastatic Hormone-sensitive Prostate Cancer: Not Yet Ready for Prime Time as the Standard of Care

Weranja K.B. Ranasinghe^a, Chad A. Reichard^b, Brian F. Chapin^{b,*}

^a Department of Urology, Orange Health Service, Orange, Australia; ^b Department of Urology, The University of Texas M.D. Anderson Cancer Centre, Houston, TX, USA

The increasing incidence of metastatic hormone-sensitive prostate cancer (mHSPC) is probably partly due to changes in screening practices and the greater sensitivity of staging modalities [1]. The current front-line treatment options for de novo metastatic PC include androgen deprivation therapy (ADT), chemohormonal therapy (ADT + 6 cycles of docetaxel; based on the CHAARTED, STAMPEDE arm C, and GETUG-AFU 15 trials), and ADT plus abiraterone for any mHSPC (based on the LATITUDE and STAMPEDE arm G clinical trials) [2–6]. Practical algorithms have been suggested to guide choices between these options for patients with high-volume metastases, but there is variability in how these systemic agents are applied in clinical practice. This issue is becoming even more complex with recent and ongoing phase 3 studies evaluating the addition of the androgen axis inhibitors enzalutamide, apalutamide, darolutamide, and orteronel in mHSPC compared to ADT alone. A complicated systemic therapy backdrop that includes inadequate understanding of the biological mechanism in prolonged responders, early castration resistance, and oligoprogression pattern differences among therapies, along with the prolonged time frames for clinical trials to mature, means that a “standard” approach to de novo metastatic PC is currently undefined. With renewed interest in treating all identifiable disease sites in the metastatic setting, there are many trials evaluating local therapy and/or metastasis-directed therapies in this patient population. There are currently data, largely in combination with ADT alone, that suggest a benefit of local radiotherapy in patients

with low-volume metastasis, but should this be the standard of care in contemporary practice [7]?

Until recently, all data on local therapy in mHSPC have been retrospective. Several of these studies have reported higher overall survival (OS) and disease-specific survival (DSS) with cytoreductive prostatectomy (CRP) compared to radiotherapy (RT), brachytherapy, or no surgical treatment, with “optimal survival benefits” seen for those with M1a disease, suggesting a role of CRP in this setting [8–11]. Whether this is purely a result of selection bias or of tumor debulking remains to be seen. We do know that CRP is a safe procedure in well-selected patients with mHSPC, with a potential for reduction of local recurrence and late local complications [12]. DSS and OS benefits have also been retrospectively demonstrated with RT to the primary tumor compared with systematic treatment or observation alone [8–11,13]. However, many of these studies had no information on the volume or location of metastases detected, used conventional imaging methods, and lacked data regarding systemic treatments.

Recently, the HORRAD study randomized 432 men with mHSPC to ADT with RT to the prostate or ADT alone [14]. This study recruited slowly over an extended time period; its power was limited by the small size and the study inclusion criteria selected more men with high-volume metastases (as reflected by median prostate-specific antigen of 142 ng/ml). The results from HORRAD favor the null hypothesis of no OS benefit with RT combined with ADT in the whole trial population at median follow-up of 47 mo. A post hoc subgroup analysis of patients with

* Corresponding author. Department of Urology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Tel. +1 713 7944166; Fax: +1 713 7944824.
E-mail address: bfcchapin@mdanderson.org (B.F. Chapin).



fewer than five osseous metastases according to a conventional bone scan very weakly favored the alternative hypothesis that RT combined with ADT provides an OS advantage. Notably, the precision of that subgroup analysis was low with a very wide confidence interval (CI) observed (hazard ratio [HR] 0.68, 95% CI 0.42–1.1).

These results were followed closely by publication of data from arm H of the STAMPEDE trial [7]. This study of 2061 men, which was well powered to address the primary endpoint and two subgroup analyses, randomized men with mHSPC to the standard of care (ADT), which changed over time to ADT ± docetaxel, or the standard of care with RT to the prostate. Consistent with HORRAD, the STAMPEDE results strongly favored the null hypotheses of no OS benefit in the population as a whole. However, a subgroup analysis of men with low-volume disease according to CHAARTED criteria showed that men receiving primary-site RT had better OS compared with those who did not receive RT (81% vs 73%; HR 0.68, 95% CI 0.52–0.90; $p = 0.007$) with a mean 3.6-mo improvement in survival at 3 yr (median not reached for either group). Interestingly, this subgroup analysis was planned before commencing data analysis, but not from the study outset.

Although the subgroup analysis of STAMPEDE arm H provides an encouraging signal of benefit derived from definitive treatment of the primary tumor with radiation in low-volume mHSPC, there are a number of key limitations that must be considered. The analysis was premature in that it was powered at 60% assuming 72-mo OS in the low-volume group, but only 25% of events had occurred at the time of reporting and only 26 patient deaths separated the two groups. Of note, subgroup analyses of trials with overall nonsignificant results are hindered by substantial inflation of type I errors, and thus the significance threshold should be appropriately adjusted, ideally to $p < 0.004$ (one-sided), to improve the probability that the difference observed is not a chance finding [15]. The generalizability of these results to the present day is also unclear, as no patient received abiraterone in addition to ADT and a minority (16%) received docetaxel. In addition, early systemic treatment resistance was not quantified. Finally, the radiation dose used in the study was less than the standard dosing (36 Gy over 6 wk in fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over 4 wk [9]). Thus, it is perhaps not surprising that there was no difference in symptomatic local progression between the groups (42% control vs 44% RT), but the authors stated that this endpoint was considered too early to assess. It is unclear why the authors deemed that the local progression data were too immature to assess (which would be expected to precede the reported OS). Both the HORRAD and STAMPEDE arm H results provide further support to ongoing trials that seek to add to the quality of the prospective data using contemporary systemic agents in combination with local therapies. RT to the primary tumor in men with low-volume mHSPC may be a consideration in the setting of ADT use alone (ie, unavailability of abiraterone and/or contraindication to docetaxel), but outside of this rare situation in contemporary practice, its benefit remains unproven and patients should be counseled regarding

ongoing equipoise in the field and the need for further information gleaned from ongoing clinical trials [16,17].

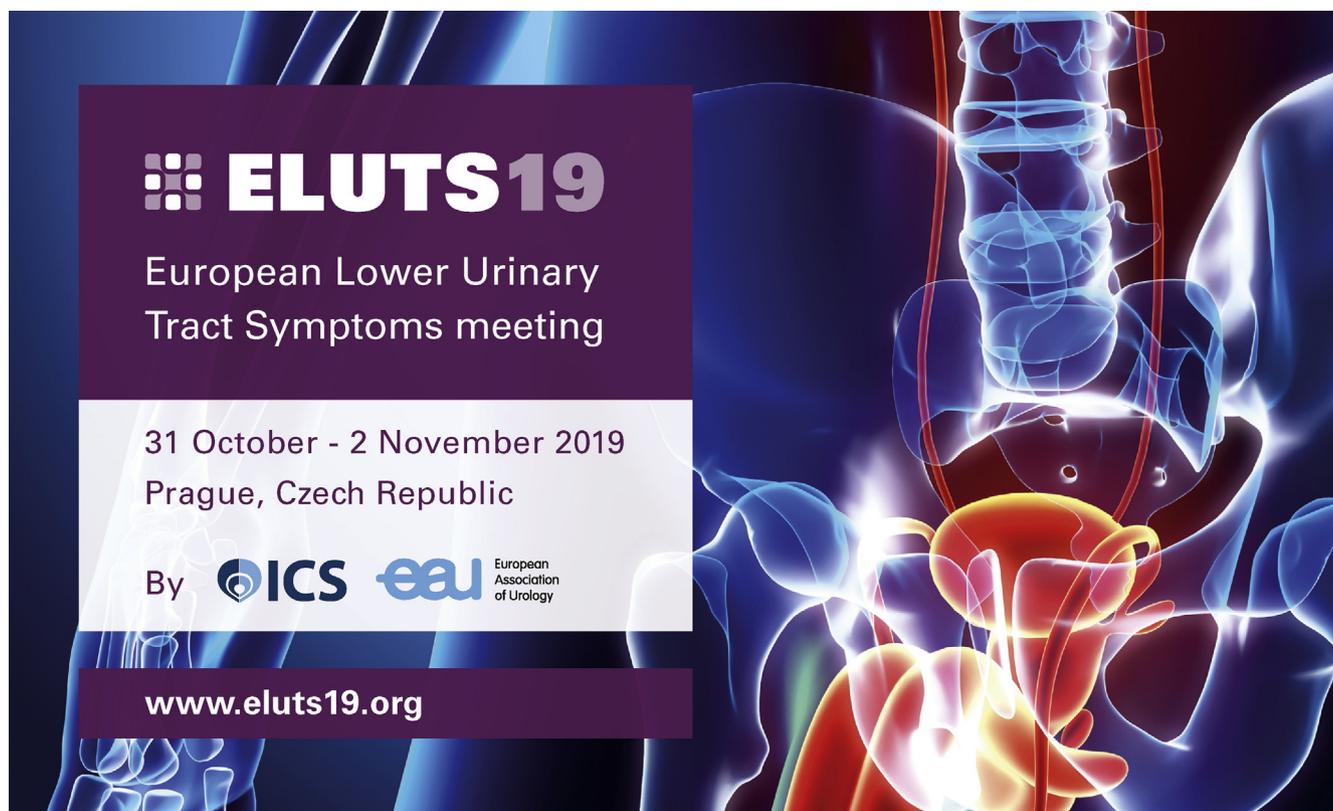
In conclusion, retrospective studies in selected patients have demonstrated a survival benefit for men receiving CRP or RT of the primary tumor in mHSPC. Recently reported subgroup analyses for randomized prospective data should be interpreted carefully in the context of current and evolving systemic therapies, the inherent inadequacy of volume-based disease classification, and an underpowered and somewhat premature analysis of the subgroup data. Taking all of these points into consideration, there is currently not enough evidence to recommend RT to the primary tumor as standard of care for patients treated with ADT + abiraterone or ADT + docetaxel, for low-volume mHSPC. In addition, given the negative findings overall for both HORRAD and STAMPEDE arm H, patients with high-volume mHSPC should not receive local therapy outside of a clinical trial unless it is strictly palliative in nature. The field is in need of biologic classifiers to more appropriately categorize and treat men with therapies specific to the inherent biologic vulnerabilities of their disease.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] Kelly SP, Anderson WF, Rosenberg PS, Cook MB. Past, current, and future incidence rates and burden of metastatic prostate cancer in the United States. *Eur Urol Focus* 2018;4:121–7.
- [2] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–46.
- [3] James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163–77.
- [4] Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14:149–58.
- [5] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352–60.
- [6] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017;377:338–51.
- [7] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018;392:2353–66.
- [8] Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol* 2014;65:1058–66.
- [9] Antwi S, Everson TM. Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. *Cancer Epidemiol* 2014;38:435–41.
- [10] Fossati N, Trinh QD, Sammon J, et al. Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed

- with metastatic prostate cancer: a SEER-based study. *Eur Urol* 2015;67:3–6.
- [11] Gratzke C, Engel J, Stief CG. Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. *Eur Urol* 2014;66:602–3.
- [12] Heidenreich A, Pfister D, Porres D. Cyoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. *J Urol* 2015;193:832–8.
- [13] Rusthoven CG, Jones BL, Flaig TW, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol* 2016;34:2835–42.
- [14] Boeve LMS, Hulshof M, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol* 2019;75:410–8.
- [15] Tanniou J, Tweel IV, Teerenstra S, Roes KC. Level of evidence for promising subgroup findings in an overall non-significant trial. *Stat Methods Med Res* 2016;25:2193–213.
- [16] UNICANCER. A phase III study for patients with metastatic hormone-naïve prostate cancer (PEACE1). <https://ClinicalTrials.gov/show/NCT01957436>.
- [17] Southwest Oncology Group. Standard systemic therapy with or without definitive treatment in treating participants with metastatic prostate cancer. <https://ClinicalTrials.gov/show/NCT03678025>.



ELUTS19
European Lower Urinary Tract Symptoms meeting

31 October - 2 November 2019
Prague, Czech Republic

By **ICS** **EAU** European Association of Urology

www.eluts19.org