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

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 410–418 of this issue

Local Treatment in Metastatic Prostate Cancer: A Cultural Shift Confronts Power and Selection

Alan Dal Pra, Matthew Abramowitz, Alan Pollack *

Department of Radiation Oncology, University of Miami Miller School of Medicine, Miami, FL, USA

Two important randomized trials testing the role of local radiotherapy (RT) in improving overall survival (OS) in metastatic prostate cancer patients have recently been reported. In the October issue of *European Urology*, Boevé et al. [1] presented the results of the HORRAD trial, which was soon followed by the results of STAMPEDE trial, arm H, by Parker et al. [2], published in *The Lancet*.

Radical treatment of the primary tumor in the presence of metastatic disease has been debated for a few decades and potentially represents a cultural shift in cancer treatment. The concept of combined primary tumor cytoreduction and systemic therapy has been attempted in different malignancies and is a focus of several contemporary prostate cancer randomized trials (Table 1). Many clinical trials have fallen on their own sword due to a failure in accounting for patient population heterogeneity and missed power estimates. Success of the trials in the Table 1 will be judged based on a number of factors, including how patients are selected (eg, extent of disease, type of systemic therapy, comorbidities, and feasibility of accrual within a time frame), power estimates to ensure a convincing result, and the overall impact on quality of life.

Stephen Paget's [3] "seed and soil" theory from 1889 and Kaplan et al.'s [4] concept of the "premetastatic niche" are consistent with the tropism of prostate cancer subclones for the microenvironment in bone as an initial hematogenous site of spread. Although prostate cancers have the potential to spread to other organs, this picture more often occurs when the metastatic tumor burden is high. As an example, prostate cancer visceral spread is associated with worse outcome and is typically a late phenomenon. Moreover, a multidirectional process has characterized the complexity of metastatic spread in prostate cancer with local-to-metastasis and metastasis-to-metastasis monoclonal or polyclonal seeding [5], mechanisms that are likely more of a factor when the tumor burden is high. In addition, RT influences the modulation of immune responses due to effects, in part, related to the balance between pro- and anti-inflammatory cytokines and chemokines [6], and which would be affected by tumor burden. A higher volume of disease has the potential to minimize the benefit of adding a local treatment to initial androgen suppression.

With a median follow-up of 47 mo, the HORRAD study reported no significant difference in OS—43 versus 45 mo in the control versus RT group (hazard ratio [HR] 0.90, 95% confidence interval [CI]: 0.70–1.14; $p = 0.4$). However, there was a significant improvement in median time to prostate-specific antigen (PSA) progression in the RT group (crude HR 0.78, 95% CI: 0.63–0.97; $p = 0.02$). Disease-specific survival and quality of life data were not reported. The HORRAD results also raised the question that survival might be improved in a subgroup of patients with a low metastatic burden, although the study was underpowered for such a subgroup analysis (HR 0.68, 95% CI 0.42–1.10).

HORRAD had insufficient power to show a difference in OS as planned. The trial was originally designed to demonstrate a 10-mo difference in median OS from 28 to 38 mo. The standard arm, however, had better than predicted survival. Interestingly, the initial sample size of 500 patients was reduced to 426 after interim analysis, although further details on the reasons for such adjustment are not provided. This concern is highlighted by the broad confidence intervals around the primary endpoint. In addition, the study lacks granularity on comorbidities,

DOI of original article: https://doi.org/10.1016/j.eururo.2018.09.008.
* Corresponding author. Department of Radiation Oncology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, 1475 NW 12th Ave, 1st floor, Miami, FL 33136, USA.
E-mail address: apollack@med.miami.edu (A. Pollack).

https://doi.org/10.1016/j.eururo.2018.11.054
0302-2838/© 2018 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Table 1 – Contemporary randomized controlled trials assessing local treatment in metastatic prostate cancer patients

Study	Study arms	Patient population	Radiotherapy dose (Gy)/no. of daily fractions	Stratification factors	Primary endpoint	Sample size
HORRAD [1]	ADT vs ADT + EBRT	≥M1a disease (any volume) on standard imaging	70/35 or 57.76/19	No stratification	OS	425
STAMPEDE arm H [2]	ADT vs ADT + EBRT	≥M1a disease (any volume) on standard imaging	55/20 or 36/6 (weekly)	• Center • Age (<70 vs ≥70 yr) • Nodal involvement (negative vs indeterminate vs positive) • WHO PS • Type of ADT • Use of aspirin or NSAID • Use of docetaxel[a]	OS	2061
PEACE-1 (NCT01957436)	ADT (SOC) vs ADT + abiraterone + prednisone vs ADT + EBRT vs ADT + abiraterone + prednisone + EBRT	≥M1a disease (any volume) on standard imaging	74/37	• Center • PS (0 vs 1–2) • Disease extent: LN only vs bone (± LNs) vs presence of visceral metastases • LHRH agonist vs LHRH antagonist vs bilateral orchiectomy	OS and PFS (CRPC PFS)	916
SWOG 1802 (NCT03678025)	SOC vs SOC + local treatment (RP or EBRT)	≥M1a disease (any volume) on standard imaging	79.2–80/44–10 or 60/20 or 36.25/5	• Time between initiation of systemic therapy and step 1 registration • RP vs EBRT • PSA level at randomization (≤4 vs >4 ng/ml) • Disease volume by standard imaging: polymetastatic (>4 sites) vs oligometastatic and no prior treatment vs oligometastatic and prior treatment	OS	1200
TRoMbone (ISRCTN15704862)	SOC vs SOC + RP	Oligometastasis (1–3 osseous lesions on standard imaging), no visceral metastases	NA	Center	Feasibility + expansion cohort (OS)	50
g-RAMPP (NCT02454543)	SOC vs SOC + RP	Oligometastasis (1–5 osseous lesions on standard imaging or PET), no visceral metastases, N1 allowed	NA	NA	PCSS	452

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; EBRT = external beam radiotherapy; LHRH = luteinizing hormone–releasing hormone; LN = lymph node; NSAID = nonsteroidal anti-inflammatory drug; OS = overall survival; PCSS = prostate cancer–specific survival; PET = positron emission tomography; PFS = progression-free survival; PS = performance status; PSA = prostate-specific antigen; RP = radical prostatectomy; SOC = standard of care; WHO = World Health Organization.

[a] Docetaxel permitted from December 2015.

age, and other competing risks, which could have further impacted the power to detect a difference in OS. Although the use of other anticancer treatments was similar in both treatment arms of deceased patients, only half of them received any sort of subsequent therapy, questioning the fitness of the population.

Approximately two-thirds of the HORRAD trial patients had more than five osseous metastases on bone scan and median PSA was 142 ng/ml, suggesting that the majority of these patients had a high tumor burden. The OS benefit due to local treatment is likely to hinge more on the burden of disease than on any other factor [7].

Selection and stratification of patients are key components of trials addressing this issue (Table 1), and details along these lines do not appear to have been accounted for in the design of the HORRAD trial. The trial included all prostate patients with primary bone metastases, without regard for other types of metastases (eg, visceral, lymph nodal, or bone beyond the axial skeleton), and there was no mention of stratification factors potentially related to OS to ensure that the arms were balanced. The STAMPEDE trial addresses a similar question; however, in contrast to HORRAD, the randomization was stratified by a number of factors and a preplanned analysis based on the metastatic burden was developed.

STAMPEDE was initially planned to accrue 1250 patients with the goal of demonstrating a 25% relative improvement (HR 0.75) in both failure-free survival and OS for the RT group. After revision for 1800 patients, the trial overaccrued, reaching 2061 patients in 3.5 yr. Patients with newly diagnosed metastatic disease on bone scan and soft-tissue imaging with a median PSA of 98 ng/ml were included. After the publication of the CHAARTED trial in 2015 [8], docetaxel was used in 20% of the study cohort. With a median follow-up of 37 mo in the STAMPEDE trial, there was no OS improvement from local RT for the entire cohort of patients with newly diagnosed metastatic prostate cancer, confirming the importance of tumor burden when local treatment is utilized.

Although not described in original protocol and not define by stratification factors, the STAMPEDE investigators hypothesized in May 2018 that the RT effect would be greater in patients with a low baseline metastatic burden, as defined by the CHAARTED study (less than four bone metastases without lesions outside of the vertebral column and pelvis, and absence of visceral metastases). It was anticipated that if approximately 40% of patients had a low metastatic burden, there would have been >90% power for failure-free survival (HR 0.70) if median failure-free survival was 24 mo in the control group and about 60% power for OS (HR 0.70) if median survival was roughly 6 yr. If approximately 60% of patients had a high metastatic burden, it was anticipated that the subgroup analysis would have roughly 88% power for failure-free survival (HR 0.80) if median failure-free survival was 12 mo in the control group and about 63% power for OS (HR 0.80) if median survival was 4 yr. Patients with a low metastatic burden, in fact, had an 8% improvement in OS (HR 0.68, 95% CI 0.52–0.90; $p = 0.007$; number needed to treat [NNT] 12). Importantly, low-volume disease was found to be a prognostic marker of OS and a predictive marker of response to localized RT. There was also an improvement in failure-free survival in the low-volume disease group treated with RT (HR 0.59, 95% CI 0.49–0.72; $p < 0.0001$; NNT 6). There was no difference between the RT schedules (daily vs weekly). RT was overall very well tolerated with low rates of acute and long-term toxicity. Similar to HORRAD, STAMPEDE did not report quality of life data.

Overall, we believe that the investigators have properly predefined the assessment of the subgroups (RT schedule [daily vs weekly] and baseline metastatic burden [low vs high]). As mentioned by the authors, the analysis met the criteria proposed by Sun et al. [9] to assess the credibility of subgroup effects. In addition, exploratory interaction tests ensured consistency of treatment effect within stratification factors, by time, Gleason score, and PSA before hormone therapy. This suggested a low likelihood that the apparent subgroup effect could be accounted for by chance.

The RT radiobiological equivalent doses in the STAMPEDE trial are below the conventional doses used in the primary treatment of prostate cancer. More contemporary RT doses and potentially pelvic nodal treatment using newer treatment techniques could further improve outcomes. Along these lines, treatment of all sites of tumor bulk in those with oligometastatic disease would directly address the metastasis-to-metastasis mechanism of spread.

The results of the STAMPEDE trial suggest that we have underestimated the systemic biological ramifications of RT for prostate cancer. It is well known that RT elicits a wide range of effects, including, but not limited to, radiation-induced antitumor immunity. Radical prostatectomy does not have the same effect. In fact, provocative experimental data suggest that surgery accelerates tumor cell dissemination, increases circulating tumor cell survival by enhancing immune evasion, enhances entrapment at metastatic sites, and increases invasion and migration capabilities to establish new metastatic foci. Surgery can also induce changes in the environment of micrometastatic disease to enhance its growth [10]. RT is cost effective, has relatively low side effects, and is available in most parts of the world. Given the encouraging data from STAMPEDE, RT should be considered the local treatment of choice in low-volume metastatic prostate cancer patients. The pending results of the PEACE-1 trial (NCT01957436) and STOPCAP M1 meta-analysis [11] may provide additional support for local RT in the context of androgen deprivation therapy, abiraterone, and docetaxel. Of note, the recently opened SWOG 1802 trial (NCT03678025) compares no local treatment with local treatment favoring prostatectomy in a similar population of men with metastasis. Whether there is equipoise between surgery and RT in this group of patients is debatable, as we have pointed out. While the ethics of having a control no-local-treatment arm in SWOG 1802 should be considered, the trial could serve to elucidate the prostatectomy versus RT question if planned and sufficiently powered. In addition, SWOG 1802 will be testing local therapy in the context of "best contemporary systemic therapy," which was not the case in STAMPEDE and HORRAD.

In conclusion, STAMPEDE offers the best available evidence on the role of local RT treatment in men with low-volume metastatic prostate cancer, which should be strongly considered for those with this new diagnosis. In addition, the findings of an increased number of lesions using new imaging modalities should not preclude the use of local RT. Nonetheless, several questions still remain, especially the comparative effectiveness of prostatectomy versus RT in men with oligometastatic disease and the role of metastasis-directed therapy.

Conflicts of interest: Dr. Dal Pra holds a research agreement with GenomeDx Biosciences. Dr. Abramowitz has received Varian Medical Systems honorarium for travel. Dr. Pollack is a coinvestigator in a Varian Medical Systems research grant.

References

[1] Boevé 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.

[2] 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. In press. https://doi.org/10.1016/S0140-6736(18)32486-3.

[3] Paget S. The distribution of secondary growths in cancer of the breast. Cancer Metastasis Rev 1989;8:98–101.

[4] Kaplan RN, Psaila B, Lyden D. Bone marrow cells in the 'pre-metastatic niche': within bone and beyond. Cancer Metastasis Rev 2006;25:521–9.

[5] Gundem G, Van Loo P, Kremeyer B, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520:353–7.

[6] Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol 2017;14:365–79.

[7] 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.

[8] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.

[9] Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:c117.

[10] Tohme S, Simmons RL, Tsung A. Surgery for cancer: a trigger for metastases. Cancer Res 2017;77:1548–52.

[11] Burdett S, Tierney J, Fisher D, et al. A systematic review and meta-analysis of the effects of radiotherapy for metastatic hormone-sensitive prostate cancer. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=96108.