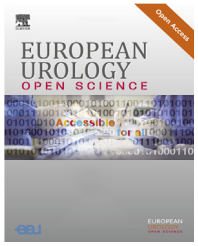
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Open Horizon – Editorial

Establishing a Role for Radical Prostatectomy in Low-volume Metastatic Disease: From Premise to Proof?

Claudia Kesch [a,b,*], *Giorgio Calleris* [a,c], *Benjamin Pradere* [a], *Guillaume Ploussard* [a]

[a] *Department of Urology, UROSUD, La Croix du Sud Hospital, Quint Fonsegrives, France;* [b] *Department of Urology and West German Cancer Center, University Hospital Essen, Essen, Germany;* [c] *Department of Urology, San Giovanni Battista Hospital, Città della Salute e della Scienza and University of Turin, Turin, Italy*

The overall survival (OS) benefit of prostate radiotherapy (RT) in oligometastatic castration-sensitive prostate cancer (CSPC) is widely accepted on the basis of results from STAMPEDE (arm H) [1] and a post hoc subanalysis of HORRAD [2]. PEACE-1 [3] is a prospective phase 3 trial in which men with de novo mCSPC (n = 1173) were randomized 1:1:1:1 to standard of care (SOC), SOC + abiraterone, SOC + RT, or SOC + abiraterone + RT. The co-primary endpoints were radiographic progression-free survival (rPFS) and OS.

Previously, the trial demonstrated that combining androgen deprivation therapy (ADT) and abiraterone in de novo mCSPC improves OS and rPFS in comparison to SOC, including SOC with or without docetaxel [4]. The updated data showed that for men with low-volume de novo mCSPC, combining prostate RT with intensified systemic treatment (abiraterone ± docetaxel) was associated with better improved rPFS and castration-resistant prostate cancer–free survival, but not with better OS. The results presented at the 2023 American Society of Clinical Oncology meeting highlighted the benefit of prostate RT on the deferred onset of serious genitourinary (GU) adverse events, irrespective of the metastatic burden. Nevertheless, the onset of serious GU adverse events and symptom progression represents a debatable endpoint with a lack of scientific background and definition. Despite the weakness of this endpoint, the investigators suggested that prostate RT could still be used in the era of doublet or triplet intensified therapy to prevent symptom progression, whereas conflicting data regarding survival benefits remain.

Local treatment with RT is therefore proposed for symptom prevention in patients with de novo mCSPC. In this context, however, we should discuss whether symptom prevention might not be even amplified with radical prostatectomy (RP).

To date, evidence on cytoreductive therapy including RP remains sparse. The randomized phase 2 FUSCC-OMPCa trial comparing ADT with or without local therapy (85% RP) found that combination therapy prolonged rPFS and OS. However, there was no specific comparison of GU adverse events [5]. The TRoMbone trial randomized patients with synchronous oligometastatic prostate cancer to ADT or ADT plus RP. Intraoperative and postoperative complications occurred in one (4.2%) and three (12.5%) patients, respectively, the incontinence rate at 6 mo was 16.7%, and there was no significant difference in EQ-5D-5L descriptive scores, suggesting that RP is feasible without a substantial impact on quality of life (QoL) [6]. The prospective LoMP trial registry compared patients with de novo mCSPC undergoing cytoreductive RP, RT, or no local therapy (NLT). Although there was no OS difference between RP and RT, both showed better OS in comparison to NLT. The RP group had significantly lower risk of local adverse events in comparison to the RT group and the NLT group, suggesting a competitive advantage of surgery over RT for local progression-related symptoms. However, patients with less advanced tumors underwent RP, limiting the comparability of the different cohorts. Moreover, contrary to the PEACE-1 data, the risk of local adverse events was not significantly lower for RT than for NLT [7]. Taken together, the results actually provide some evidence indicating that RP might not only prevent local events but could also even improve survival.

Should this not be premise enough to establish a role for RP in low-volume mCSPC? The above data are limited by cohort size and a partial lack of randomization and are prone to a historical bias, as ADT alone is no longer the preferred systemic therapy for mCSPC. Thus, the evidence we have is becoming obsolete in the era of combination

* Corresponding author. Department of Urology, University Hospital Essen, Hufelandstrasse 55, Essen 45147, Germany. Tel. +49 201 72384969.
E-mail address: claudia.kesch@uk-essen.de (C. Kesch).

https://doi.org/10.1016/j.euros.2023.11.001

systematic therapy. This reminds us of the CARMENA paradigm, as the study assessed the role of cytoreductive nephrectomy in metastatic kidney cancer for patients treated with antiangiogenic agents, whereas contemporary management of metastatic renal cell carcinoma uses immunotherapy and combined therapies.

However, the SWOG 1802 trial (NCT03678025) will provide us with some phase 3 evidence. SWOG 1802 randomizes men with de novo mCSPC to SOC with or without definitive prostate treatment (surgery or radiation). The primary endpoint is OS, but several additional outcomes will also be assessed, including PFS, QoL, and the need for intervention for obstructive-type symptoms. While this trial will finally provide some up-to-date surgical data and will probably answer whether surgery is an appropriate option in selected candidates, a selection bias will most likely limit us in comparing RT and RP. Trying to overcome this limitation, the prospective phase 2 LomP II trial (NCT03655886) will tackle the obstacle of randomization and evaluate the feasibility of randomly assigning patients to cytoreductive prostatectomy or cytoreductive prostate irradiation.

Finally, we need to acknowledge that all our treatment approaches might need to be reconsidered with regard to molecular imaging. It was demonstrated that prostate-specific membrane antigen positron emission tomography/computed tomography is superior to conventional imaging for staging of primary prostate cancer [8] and it has since been integrated into routine clinical care in many countries. This challenges the established classification of low-volume and high-volume mCSPC. It also expands the discussion once again towards extended local therapy (eg, RP with extended pelvic lymphadenectomy or whole pelvis radiation) and metastasis-directed therapy to prolong OS or even provide a cure.

In addition to the impact of primary treatment on oncologic outcomes, PEACE-1 might have established a role for local RT to prevent serious GU-related adverse events in mCSPC. This fuels the debate on the potential benefit of surgery, as this local treatment can provide at least the same benefit as RT and may be better in preventing obstructive complications. The results from SWOG 1802 are now eagerly awaited for further insights into the potential benefits of RP in selected mCSPC patients.

Conflicts of interest: The authors have nothing to disclose.

References

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

[2] Boevé LMS, Hulshof MCCM, 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. https://doi.org/10.1016/j.eururo.2018.09.008.

[3] Bossi A, Foulon S, Maldonado X, et al. Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): results of PEACE-1, a phase 3 randomized trial with a 2x2 design. J Clin Oncol 2023;41(17 Suppl):LBA5000. https://doi.org/10.1200/jco.2023.41.17_suppl.LBA5000.

[4] Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet 2022;399:1695–707. https://doi.org/10.1016/S0140-6736(22)00367-1.

[5] Dai B, Zhang S, Wan FN, et al. Combination of androgen deprivation therapy with radical local therapy versus androgen deprivation therapy alone for newly diagnosed oligometastatic prostate cancer: a phase II randomized controlled trial. Eur Urol Oncol 2022;5:519–25. https://doi.org/10.1016/j.euo.2022.06.001.

[6] Sooriakumaran P, Wilson C, Rombach I, et al. Feasibility and safety of radical prostatectomy for oligo-metastatic prostate cancer: the Testing Radical prostatectomy in men with prostate cancer and oligo-Metastases to the bone (TRoMbone) trial. BJU Int 2022;130:43–53. https://doi.org/10.1111/bju.15669.

[7] Lumen N, De Bleser E, Buelens S, et al. The role of cytoreductive radical prostatectomy in the treatment of newly diagnosed low-volume metastatic prostate cancer. Results from the Local Treatment of Metastatic Prostate Cancer (LoMP) registry. Eur Urol Open Sci 2021;29:68–76. https://doi.org/10.1016/j.euros.2021.05.006.

[8] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16. https://doi.org/10.1016/S0140-6736(20)30314-7.