The emerging role of local therapy in metastatic prostate cancer

Nora Sundahl, Alison Tree, Chris Parker

Guidelines: 2000-4000 words; max 1 fig & 2 tables

1. Introduction

Local therapy was long assumed to be unable to impact the disease course in patients with metastatic prostate cancer and therefore was considered only for palliative reasons. The central dogma remained that only systemic treatments are able to alter the disease course in patients with metastatic cancer. Retrospective analyses[1-6] however suggested that radical treatment of the local prostate tumor, or of the metastases, might prolong survival with limited side effects.

Recent prospective data has established a paradigm shift by unequivocally showing a survival benefit for local prostate radiotherapy in patients with metastatic disease. This article summarizes current prospective clinical evidence regarding local therapy in metastatic prostate cancer.

2. Rationale

The primary tumor is key in the development of metastatic disease as it not only sheds cancer cells able to spread elsewhere in the body, it may also facilitate the metastatic process by creating 'premetastatic niches'.[7,8] Via the secretion of cytokines, the primary tumor might recruit bone marrow-derived cells to home to distant organs and prepare these microenvironments to become receptive for future metastases.[8-12] Furthermore, after the formation of metastases, it is hypothesized that intricate communication between the primary and the metastases allows for the latter to continue to grow and prevents them from becoming dormant.[13] This led to the hypothesis that eradicating the primary tumor might not only have a local effect, but also a systemic effect by preventing future metastases and by hampering already established distant disease.[8,14,15] Additionally, whole-genome sequencing has revealed that cancerous spread not only occurs from the primary tumor, but also from metastasis-to-metastasis.[16] By abrogating this pathway, radical treatment of metastatic lesions could therefore also potentially alter the course of the disease.

3. Current clinical evidence
    a. Primary tumor

The recent results from the STAMPEDE trial[17] are the first to show unequivocally that treatment of the primary tumor can impact overall survival. In this trial, 2061 patients with newly diagnosed metastatic hormone-sensitive prostate cancer were randomized to receive either standard of care, (which was androgen deprivation therapy (ADT) or ADT and docetaxel after December 2015), or standard of care in combination with radiotherapy to the prostate (55 Gray [Gy] in 20 fractions over four weeks or 36 Gy in six fractions over six weeks). If the patient was to receive both docetaxel and local prostate radiotherapy, the former was administered first, with radiotherapy starting 3 to 4 weeks after the last dose of docetaxel. The addition of radiotherapy resulted in a 3-year survival improvement of 73% to 81% in patients with low volume disease. This benefit was not seen in patients with high volume disease, nor for the whole, unselected group of patients. Importantly, the subgroup analysis indicating benefit in the low volume disease group met all criteria proposed by Sun et al.[18] in order to be considered a credible result. Furthermore, radiotherapy was well-tolerated, with no grade 5 adverse events, and with grade 3 or 4 RTOG acute effects noted in 5% of patients at any point during follow up. Patients who received the weekly regimen experienced less grade 1-4 acute effects than those receiving the daily schedule. Only a small minority of patients experienced grade 3-4 RTOG late effects, namely 4% of the radiotherapy arm, as compared to 1% in

the control arm. Of note, no significant difference with regards to the survival benefit was observed between the daily or weekly radiotherapy regimen.[17]

The HORRAD trial was a similar trial that randomized a total of 432 patients with metastatic hormone-sensitive prostate cancer to either ADT only or ADT with radiotherapy to the primary tumor (70 Gy in 35 fractions over 7 weeks or 57.76 Gy in 19 fractions over 6 weeks). This trial was negative, showing no survival benefit of radiotherapy for the unselected group of patients. A subgroup analysis based on number of bone metastases suggested a favorable effect of radiotherapy in the group with fewer than five lesions, but no significant interaction was noted.[19]

A subsequent meta-analysis of the data of both the above trials confirmed the benefit of local radiotherapy in men with low-volume disease, with a 7% improvement in 3-year survival.[20] Again, no survival benefit was noted in the whole unselected group of patients.

Consequently, these findings show that in patients with low volume metastatic prostate cancer, radiotherapy to the primary tumor should now be part of the standard of care. Furthermore, given both patients with localized disease confined to the prostate, and patients with limited metastatic disease benefit from prostate radiotherapy, it can be assumed that patients with disease spread solely to the pelvic lymph nodes should also benefit from prostate radiotherapy, and potentially from pelvic nodal radiotherapy as well. Besides systemic therapy, these patients should therefore also be offered local prostate radiotherapy and pelvic nodal irradiation in most cases.

It is important to note that these trials only assessed the role of prostate radiotherapy, and not of prostatectomy or other local treatments. Whether or not surgery and radiotherapy are equivalent with regards to survival benefit, as well as toxicity, in this population is currently still under investigation.[21] Aside from potentially more surgery-related side effects in this, on average, older population,[22] radiotherapy could potentially elicit additional, systemic effects besides local ablation.[23] Therefore, until it has been proven that surgery is non-inferior to radiotherapy in this setting, radiotherapy should be recommended to these patients.

b. Patient selection

Importantly, given that local radiotherapy to the primary is only advantageous in patients with low volume disease, the definition of the latter is of utmost importance to ensure that no patients are denied a treatment from which they might benefit. To determine tumor burden, the STAMPEDE trial used the CHAARTED criteria, based on CT and bone scan, which states that 'high volume' entails at least four bony metastases (of which at least one is outside the spine or pelvis) and/or visceral metastasis. All other patients not meeting these criteria were designated as 'low volume'.[17,24] Conversely, the meta-analysis combining both the STAMPEDE data with the HORRAD data, defined 'low volume' disease as four or fewer bone metastases, given that the data available on the HORRAD patients did not allow them to be classified according to the CHAARTED criteria.[20]

Most probably there is a large overlap between patients regarded as low volume as per the CHAARTED definition and those having ≤4 bone metastases. Nonetheless, there are some discrepancies between the two classifications, given that patients with numerous spinal metastases only would have been regarded as low volume as per the CHAARTED criteria, yet as high volume as per the definition used in the meta-analysis.

Given that a benefit was noted in both groups of low volume disease, and considering that local radiotherapy to the prostate was well-tolerated,[17] a reasonable option would be to consider this treatment for all patients who fit at least one of the definitions of low volume disease.

In light of this, it should be noted that patients in these trials were conventionally imaged using computed tomography (CT) or magnetic resonance imaging (MRI), and bone scan in the STAMPEDE trial, or bone scan only in the HORRAD trial.[17,19] When using more sensitive imaging modalities, e.g. prostate-specific membrane antigen positron emission-tomography-CT (PSMA PET-CT), in this patient cohort, the detectable tumor burden will likely be higher than when imaged conventionally. This could potentially lead to patients not receiving local treatment, while they would actually benefit from it. Moreover, in the time PSMA PET-CT was used in a diagnostic setting, and prior to the publication of the STAMPEDE trial, it is most likely that some patients who would not have been metastatic on conventional imaging, and hence should have received local treatment, did show limited metastases on PSMA PET-CT and hence were denied localized treatment. More sensitive imaging in this case most probably led to the undertreatment of some patients. Clear evidence supporting the use of PSMA PET-CT in newly diagnosed prostate cancer patients remains awaited, and for the time being the results of these images should therefore be interpreted with caution.

Furthermore, it is important to note that the significance of nodal disease volume is currently unknown, as both definitions of disease volume completely disregard it. Hence, a patient with large tumor burden in lymph nodes only, would still be regarded as low volume. Future research elucidating the importance of nodal disease volume therefore remains necessary.

c. Metastasis

The STOMP trial was the first prospective trial to hint that local treatment of metastases might be beneficial in patients with oligometastatic disease.[25] In this phase 2 trial, patients with a biochemical relapse with three or less extracranial metastases after radical prostate cancer treatment, were randomized to either metastasis-directed therapy or surveillance, the standard of care at time of the trial. The primary endpoint was met, with a median ADT-free survival of 21 months in the experimental arm, as compared to 13 months in the control arm.

Similarly, the SABR-COMET basket trial, which allowed patients with up to 5 metastases from a variety of solid tumors including prostate cancer, investigated stereotactic body radiotherapy (SBRT) to all metastases in a randomized controlled manner. In total, 99 patients were enrolled, of whom 33 were randomized to the control arm and 66 to the SBRT arm. A significant improvement in survival was noted, with a median overall survival of 41 months after SBRT as compared to 28 months in the control group.[26] However, toxicity was surprisingly high with three out of 66 patients in the interventional arm experiencing grade 5 toxicity. Of note, 6% of the control arm and 21% of the SBRT arm were prostate cancer patients. Even though this data is from a relatively small patient group and not solely from prostate cancer patients, it is intriguing and warrants further investigation.

In line with this, the trial by Gomez et al. investigated local therapy in patients with non-small-cell lung cancer and maximally three metastases visible after frontline chemotherapy.[27,28] Median overall survival was again significantly prolonged to 41 months as compared to 17 months in the control group. Yet in contrast to the SABR-COMET trial, no grade 4 or higher toxicity was observed.

Combined, these data have suggested that radical treatment of visible disease in oligometastatic prostate cancer patients might be beneficial. Yet given the lack of phase 3 data, treatment of oligometastases should not be current standard of care and hence should only be considered within

the setting of a clinical trial. The newly approved STAMPEDE arm will address this question and elucidate the impact of metastasis-directed therapy in the setting of low volume hormone-sensitive metastastic prostate cancer (Nicholas van As, personal communication).

Besides oligometastatic patients, oligoprogressive patients, i.e. patients with a limited number of progressing lesions, could also potentially benefit from the addition of metastasis directed therapy. Given that the oligoprogressive lesions might contain the clones most likely to disseminate elsewhere, and hence drive the future disease course , treating them might retard progression and prolong survival. The current ongoing phase 2 TRAP trial (NCT03644303) investigates the addition of SBRT to patients with hormone therapy-relapsed prostate cancer progressing on second line hormonal treatment with maximally two progressing lesions. This will be the first trial to investigate whether local treatment of oligoprogressive disease – and regardless of total tumor burden – could be beneficial.[29]

In the hormone therapy-relapsed setting, Kwon et al. conducted a phase 3 trial of ipilimumab compared to placebo after radiotherapy (one fraction of 8 Gy) to 1-5 bone metastases.[30] No selection was made based on number of visible or progressing lesions. Even though prostate cancer is notorious for being a non-immunogenic tumor type,[31] the underlying idea was that the addition of radiotherapy to ipilimumab would facilitate a systemic anti-tumor immune response via the release of tumor-specific antigen and stimulation of an inflammatory tumor microenvironment.[32] Unfortunately, no difference was noted in overall survival between both arms. This lack of benefit is presumably due to a combination of factors, i.e. the relatively non-immunogenic tumor type, combined with a less potent checkpoint inhibitor and a single fraction of radiotherapy prior to start of immunotherapy. Regarding the latter, subsequent research showed that repeated fractions of hypofractionated radiotherapy (e.g. 24 Gy in three fractions) concurrent with checkpoint inhibitors seems most promising in eliciting an immune effect.[33,34] Hence, it is not excluded that radiotherapy might aid in prostate cancer patients to elicit a systemic anti-tumor immune effect, yet this is perhaps more likely when administered at a different dose and combined with a more potent checkpoint inhibitor (i.e. anti-programmed cell death protein 1), and - most importantly - only in selected patients at the higher end of the immunogenicity spectrum.

Furthermore, given both arms in this trial received radiotherapy to metastatic disease, the effect of this localized treatment cannot be assessed. Yet, since overall survival was shorter than expected in both arms, radiotherapy most likely did not have a major impact on disease course. Even though it is unclear whether some patients had all visible metastases irradiated, the palliative dose (one fraction of 8 Gy) would have also been too low to have a local ablative effect.

4. Search for predictive biomarkers

As is now evident, local radiotherapy to the prostate can be beneficial in patients with metastatic hormone-sensitive prostate cancer, with tumor volume being an indicator for selecting who will benefit. However, even though the group with low volume prostate cancer benefits from local radiotherapy, a small proportion of these patients nevertheless progress rapidly with a limited overall survival. This was also seen in the STOMP-trial, where a small subset of patients with initial oligometastatic disease had rapidly progressive disease following radical treatment of all visible metastases.[17,25] Hence, even though tumor volume and location of metastases is a phenotypical representation of the underlying cancer biology, it is by itself insufficient to pinpoint exactly who will benefit from local treatment and who will not. Additional immunohistochemical or genomic biomarkers might aid in identifying who has aggressive disease at risk of disseminating quickly; as it might be that these patients would benefit from more intensified systemic therapies.

Evidence shows that prostate cancer with *TP53* or DDR gene mutations exerts a more aggressive phenotype, whilst *SPOP* mutations imply a more favorable prognosis. It might for instance be that patients with DDR gene mutations do not benefit from local radiotherapy, yet necessitate additional systemic treatments to keep the cancer in check, e.g. via use of PARP inhibitors or immunotherapy, given evidence has shown that these patients have an increased chance of responding to these treatments.[35,36] Or, alternatively, that the combination of radiotherapy with immunotherapy in these patients elicits a systemic anti-tumor immune response. Furthermore, circulating tumor DNA (ctDNA) measured in the peripheral blood could prove to be a convenient aid to elucidate the full genomic tumor profile, in both the castrate-sensitive as well as the hormone therapy-relapsed setting.[35,37-39] Also promising results have been noted in the area of proteomics which could provide a more comprehensive picture of functional cancer biology, as it not merely illustrates genomic alterations, but also changes that take place on a posttranslational level.[40]

Future advances in these fields will hopefully help in the development of patient-tailored treatments with the highest chance of response whilst avoiding unnecessary toxicity.

5. Conclusion

To conclude, radiotherapy to the primary should now be standard of care in newly diagnosed patients with low volume metastatic hormone-sensitive prostate cancer. Early clinical data suggests that local therapy of oligometastases might be beneficial, though larger, randomized controlled trials are awaited. Patient selection as to who might benefit from local treatment remains key, and future biomarkers might provide additional information, complementary to clinical patient and cancer characteristics.

References

1. 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(6):1058-1066.

2. 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(1):3-6.

3. Gratzke C, Engel J, Stief CG. Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. Eur. Urol. 2014;66(3):602-603.

4. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(24):2835-2842.

5. Ost P, Bossi A, Decaestecker K, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. Eur. Urol. 2015;67(5):852-863.

6. Decaestecker K, De Meerleer G, Ameye F, et al. Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial. BMC Cancer. 2014;14:671.

7. Kaplan RN, Riba RD, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature. 2005;438(7069):820-827.

8. Morgan SC, Parker CC. Local treatment of metastatic cancer--killing the seed or disturbing the soil? Nature reviews. Clinical oncology. 2011;8(8):504-506.

9. Psaila B, Lyden D. The metastatic niche: adapting the foreign soil. Nature reviews. Cancer. 2009;9(4):285-293.

10. Erler JT, Bennewith KL, Cox TR, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. Cancer Cell. 2009;15(1):35-44.

11. Hiratsuka S, Watanabe A, Aburatani H, Maru Y. Tumour-mediated upregulation of chemoattractants and recruitment of myeloid cells predetermines lung metastasis. Nat. Cell Biol. 2006;8(12):1369-1375.

12. Padua D, Zhang XH, Wang Q, et al. TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. Cell. 2008;133(1):66-77.

13. Giancotti FG. Mechanisms governing metastatic dormancy and reactivation. Cell. 2013;155(4):750-764.

14. Gužvić M, Klein CA. The Biology of Cancer Metastasis. In: Molls M, Vaupel P, Nieder C, Anscher MS. The Impact of Tumor Biology on Cancer Treatment and Multidisciplinary Strategies. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009.

15. Liu Q, Zhang H, Jiang X, Qian C, Liu Z, Luo D. Factors involved in cancer metastasis: a better understanding to "seed and soil" hypothesis. Mol. Cancer. 2017;16(1):176.

16. Gundem G, Van Loo P, Kremeyer B, et al. The evolutionary history of lethal metastatic prostate cancer. Nature. 2015;520(7547):353-357.

17. 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 (London, England). 2018;392(10162):2353-2366.

18. 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.

19. 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(3):410-418.

20. Burdett S, Boeve LM, Ingleby FC, et al. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. Eur. Urol. 2019;76(1):115-124.

21. Cytoreductive Prostatectomy Versus Cytoreductive Prostate Irradiation as a Local Treatment Option for Metastatic Prostate Cancer: a Multicentric Feasibility Trial (LoMP II). 2018; https://clinicaltrials.gov/ct2/show/NCT03655886.

22. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. The New England journal of medicine. 2016;375(15):1415-1424.

23. Formenti SC, Demaria S. Systemic effects of local radiotherapy. The Lancet. Oncology. 2009;10(7):718-726.

24. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. The New England journal of medicine. 2015;373(8):737-746.

25. Ost P, Reynders D, Decaestecker K, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(5):446-453.

26. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet (London, England). 2019;393(10185):2051-2058.

27. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. The Lancet. Oncology. 2016;17(12):1672-1682.

28. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(18):1558-1565.

29. Patel PH, Palma D, McDonald F, Tree AC. The Dandelion Dilemma Revisited for Oligoprogression: Treat the Whole Lawn or Weed Selectively? Clinical oncology (Royal College of Radiologists (Great Britain)). 2019.

30. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. The Lancet. Oncology. 2014;15(7):700-712.

31. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500:415.

32. Herrera FG, Bourhis J, Coukos G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. CA Cancer J. Clin. 2017;67(1):65-85.

33. Vanpouille-Box C, Alard A, Aryankalayil MJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun. 2017;8:15618.

34. Sundahl N, Vandekerkhove G, Decaestecker K, et al. Randomized Phase 1 Trial of Pembrolizumab with Sequential Versus Concomitant Stereotactic Body Radiotherapy in Metastatic Urothelial Carcinoma. Eur. Urol. 2019;75(5):707-711.

35. Vandekerkhove G, Struss WJ, Annala M, et al. Circulating Tumor DNA Abundance and Potential Utility in De Novo Metastatic Prostate Cancer. Eur. Urol. 2019;75(4):667-675.

36. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N. Engl. J. Med. 2015;373(18):1697-1708.

37. Belic J, Graf R, Bauernhofer T, et al. Genomic alterations in plasma DNA from patients with metastasized prostate cancer receiving abiraterone or enzalutamide. Int. J. Cancer. 2018;143(5):1236-1248.

38. Annala M, Vandekerkhove G, Khalaf D, et al. Circulating Tumor DNA Genomics Correlate with Resistance to Abiraterone and Enzalutamide in Prostate Cancer. Cancer Discov. 2018;8(4):444-457.

39. Romanel A, Tandefelt DG, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. Sci. Transl. Med. 2015;7(312):312re310-312re310.

40. Latonen L, Afyounian E, Jylhä A, et al. Integrative proteomics in prostate cancer uncovers robustness against genomic and transcriptomic aberrations during disease progression. Nat Commun. 2018;9(1):1176.