

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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The Role of Radiation Treatment in Metastatic Prostate Cancer



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H&O What is the evidence to support irradiation of the primary tumor in metastatic prostate cancer?

BK The main evidence comes from the STAMPEDE trial, which is a large study with multiple arms that has been a powerhouse in terms of prostate cancer research and our understanding of treatment options. Arm H of STAMPEDE randomly assigned 2061 men with newly diagnosed, untreated metastatic prostate cancer to either standard-of-care treatment with androgen deprivation therapy (ADT) or standard-of-care treatment plus radiation therapy to the prostate.

Although the study did not show a statistically significant benefit in overall survival (OS) across the whole group resulting from the addition of prostate radiation therapy, the researchers did find an increase in OS (hazard ratio, 0.68) with radiation therapy in the patients who had a low metastatic burden. In addition, an improvement in failure-free survival was noted with the use of radiation therapy in the patients who had a low metastatic burden.

The HORRAD study (N=432), which Boevé and colleagues published in 2019, similarly failed to find an improvement in OS with radiation therapy. This study, however, pooled patients with high- and low-volume metastatic disease and had a smaller percentage of participants with few metastases. Burdett and colleagues conducted a pooled analysis of the data from STAMPEDE and HORRAD, finding a 7% improvement in 3-year survival in men with fewer than 5 bone metastases. Their study does a nice job of showing that the same trend toward benefit in men with a low metastatic burden existed in HORRAD, but it was not statistically significant because HORRAD was smaller than STAMPEDE and had fewer patients with low-volume disease.

H&O Can a low bone metastatic burden be considered a predictive biomarker for response to radiation to the primary tumor?

BK Although I think we still need more information, many of us are using a low bone metastatic burden that way in practice. Having a low overall burden of disease, as evidenced by a low number of metastases, does appear to be predictive of response. The original STAMPEDE/CHAARTED definition of low metastatic burden was complicated; it generally encompassed 1 to 3 bone metastases but allowed 4 if they were limited to locations within the spine or pelvis. Other analyses of the STAMPEDE data have shown the strongest positive effect of prostate radiation therapy to be in men with 1 to 3 metastases, although men who have more may also benefit—to a lesser degree. Currently in my practice, I consider disease in men with fewer than 5 bone lesions to be low volume on the basis of the Burdett pooled analysis I described earlier, in which having fewer than 5 metastases was associated with a greater likelihood of benefit from prostate radiotherapy.

H&O Why is radiation beneficial in low-burden but not high-burden metastatic disease?

BK In my mind, the reasons are 2-fold. First, for local therapy to be effective, we need to have a systemic therapy that is quite good at controlling microscopic metastases. Luckily, we have great systemic therapy options for prostate cancer. Second, although ADT is an excellent treatment for men with newly diagnosed castration-sensitive prostate cancer, prostate cancer cells can eventually become resistant to androgen deprivation. Statistically speaking, a resistant clone is most likely to develop in

the location with the most cancer cells, which can then seed new castration-resistant metastases. If the burden of metastatic disease is low, local management of the primary tumor through the use of radiation therapy can therefore be helpful in preventing the development of further metastases from that site. In contrast, after disease has spread widely throughout the body, the prostate is less likely to be the source of metastases. As a result, radiation is less likely to prevent the development of secondary metastases.

H&O Can you discuss the use of the automated bone scan index as a predictor of response to radiotherapy?

BK You are referring to the recent study by Ali and colleagues in the *European Urology Oncology*. The bone scan was the study of choice that researchers used to diagnose prostate cancer and evaluate metastases in patients who were being enrolled in STAMPEDE. The automated bone scan index was designed to provide a score for volume of disease that could be used as a radiographic biomarker to predict the likelihood of primary outcomes. The STAMPEDE researchers looked at the volume of hotspots on the bone scan, divided them by the overall volume of the skeleton, and came up with a score. The score proved to be a useful predictor of survival; patients whose scores fell into the quartile with the smallest volume of disease were most likely to exhibit improvements in OS and failure-free survival.

H&O Would you say that irradiation of the primary tumor is now the standard of care in patients who have low-volume metastatic disease?

BK I may be a bit biased because I am a radiation oncologist, but my answer is yes. STAMPEDE created the standard for the use of abiraterone in metastatic disease, and arm H of STAMPEDE has set up irradiation as a new standard of care in patients with low-volume metastatic disease. Although this study has been criticized for being a subgroup analysis, the number of patients was sufficient (819 patients with a low metastatic burden). The size of the subset analysis is consistent with that in other phase 3 trials.

H&O What are the disadvantages of adding radiation therapy to treatment in these men?

BK You never get something for nothing, and some of the disadvantages warrant a conversation between the radiation oncologist and the patient to decide if prostate

therapy is the right next step for that patient. Two disadvantages are financial cost and time cost. In STAMPEDE, patients were required to undergo 20 treatments over a 4-week period. That meant being tied to the radiation clinic to undergo treatments, which could entail time off from work and time away from family.

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Regarding side effects, patients tend to do very well on this treatment because we use a moderate radiation dose that is intended to reduce metastasis, rather than a high radiation dose with the intention of curing disease. The majority of patients experience acute grade 1 or 2 urinary bother or gastrointestinal distress, such as tenesmus or increased bowel frequency, but patients rarely experience anything more severe. Only 6% of patients in STAMPEDE had grade 3 or higher acute toxicity, which was mostly urinary. One-third of patients had no acute toxicity. Few patients experienced late toxicity; the rate of grade 3 or 4 late toxicity was 4% for genitourinary and gastrointestinal toxicity combined.

H&O What radiation regimen should be used in these patients?

BK Because the evidence in standard of care is based on STAMPEDE, I recommend that treatment follow the STAMPEDE dose schedule of 55 Gy in 20 fractions until we have new data that suggest otherwise.

H&O Should abiraterone plus prednisone be used in conjunction with radiation therapy and ADT?

BK Yes, I think that all of these therapies can be used together. If you are following best practice for the management of metastatic disease, you need to add abiraterone. If you are following best practice for the management of local disease, you need to add radiation. STAMPEDE has also established the benefit of adding abiraterone and

prednisone to traditional ADT in men with newly diagnosed metastatic prostate cancer. We conducted a study at Duke in which we combined abiraterone, ADT, and radiation for men with high-risk nonmetastatic prostate cancer. The results, which I presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2018, showed that adding radiation therapy can reduce the duration of ADT. Although my study was a small, single-arm trial conducted in patients with high-risk nonmetastatic prostate cancer, the results supported a synergistic effect from combining abiraterone, radiation therapy, and ADT.

H&O Should men with metastatic prostate cancer receive radiation to the metastases?

BK That is an area of debate and in need of additional research. The ORIOLE trial from Phillips and colleagues at Johns Hopkins, which was published in *JAMA Oncology* in 2020, looked at radiation treatment in oligometastatic prostate cancer. A new arm of STAMPEDE is going to be studying that question, as is a phase 3 study from the ECOG-ACRIN Cancer Research Group (NCT04423211). NRG Oncology is also developing a trial in this space, which has not yet been approved. Multiple consensus guideline statements mention radiotherapy to the metastases as a treatment option, but one that needs further research.

H&O What other important studies are looking at the role of radiation treatment in metastatic prostate cancer?

BK A couple of interesting studies are coming out of Europe. One of the original studies that prompted the interest in treating oligometastatic prostate cancer with radiation therapy was the STOMP trial from Ost and colleagues in Belgium. The same investigators are now looking at the question of how to manage lymph node metastases. Which is better—highly focused treatment just to the offending lymph node or treatment that covers a wider field? This international study is currently enrolling patients (NCT03569241). Additional studies of interest are a US trial that is combining new systemic therapy agents with novel radiotherapy agents (NCT04423211) and a clinical trial, called RROPE, from the Huntsman Cancer Institute that is looking at radium therapy in men with oligometastatic disease (NCT03304418). This is a fascinating trial, and I am looking forward to seeing the results.

H&O What important questions remain to be answered?

BK We still need a clinically versatile and more-precise definition of what counts as low-volume or oligometastatic disease. We are working with rough parameters, so we need better definition and qualification. For example, the original analysis of STAMPEDE defined low-volume disease as 1 to 3 bone metastases, whereas the later sub-analysis defined it as 1 to 4 bone metastases. In addition, studies so far have not looked at the number of lymph node metastases these patients have. A patient with no lymph node disease and 1 bone metastasis is presumably very different from a patient with 20 positive lymph nodes and 1 bone metastasis. It may also be possible to use biological factors to predict how certain patients will respond to ADT and determine their risk category. For example, why does one patient's cancer metastasize in a shotgun pattern and another's in a step-by-step pattern? The answer to that may play a role in determining which patients will benefit from an escalation of systemic treatment vs a delay of systemic treatment with a focus on focal therapy.

Disclosure

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Suggested Readings

Ali A, Hoyle AP, Parker CC, et al. The automated bone scan index as a predictor of response to prostate radiotherapy in men with newly diagnosed metastatic prostate cancer: an exploratory analysis of STAMPEDE's "M1|RT comparison". *Eur Urol Oncol.* 2020;3(4):412-419.

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(3):410-418.

Burdett S, Boevé LM, Ingleby FC, et al; STOPCAP M1 Radiotherapy Collaborators. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol.* 2019;76(1):115-124.

Koontz BF, Hoffman KE, Healy P, et al. Phase II trial of 6 months ADT/abiraterone acetate plus prednisone (AAP) and definitive radiotherapy (AbiRT) for men with intermediate to high risk localized prostate cancer [ASCO abstract 11] *J Clin Oncol.* 2018;36(6)(suppl).

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. *J Clin Oncol.* 2018;36(5):446-453.

Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumor for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *The Lancet.* 2018;392(10162):2353-66.

Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol.* 2020;6(5):650-659.

Reza M, Bjartell A, Ohlsson M, Kaboteh R, Wollmer P, Edenbrandt L, Trägårdh E. Bone Scan Index as a prognostic imaging biomarker during androgen deprivation therapy. *EJNMMI Res.* 2014;4:58. doi:10.1186/s13550-014-0058-y.