Editorial Commentary

Potential biological and clinical benefit of prostate-directed interventions in patients with metastatic prostate cancer

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Novel evidence on prostate radiotherapy for metastatic prostate cancer

In a recent issue of the Lancet, Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators, Parker *et al.* (1) reported the updated results of a large prospective randomized control trial (RCT) that attempted to compare the additional radiotherapy with androgen deprivation therapy (ADT) and docetaxel for metastatic prostate cancer (mPCa). In this study, 2,061 men with mPCa were randomly assigned in a 1:1 ratio to receive ADT and docetaxel or ADT and docetaxel with radiotherapy and confirmed that addition of radiotherapy substantially improved failure-free survival [adjusted hazard ratio (HR), 0.76; 95% confidence interval (CI), 0.68–0.84; P<0.0001] but not overall survival (HR, 0.92; 95% CI, 0.80–1.06; P=0.27) in all patients. Subgroup analysis according to metastatic burden at randomization was prespecified in this RCT. High metastatic burden was defined as ≥4 bone metastases with at least one metastatic lesion outside the vertebral bodies, pelvis, or viscera. All other patients who were evaluable by imaging exams were considered to have low metastatic burden (2). In a subgroup of patients with low metastatic burden, additional radiotherapy had improved overall survival (adjusted HR, 0.68; 95% CI, 0.52–0.90), whereas a significant benefit of prostate radiotherapy was not observed in patients with high metastatic burden (adjusted HR, 1.07; 95% CI, 0.90–1.28).

Regarding the dose schedule of radiotherapy to prostate, either one of the two hypofractionated dose schedule of external-beam radiotherapy was selected before randomization: 36 Gy in 6 fractions or 55 Gy in 20 fractions. These hypofractionated schedules were unique to this RCT because recommended dose schedules of radical radiotherapy for localized PCa involves 74–80 Gy. In a prior RCT evaluated benefit of additional radiotherapy to mPCa with bone metastasis, namely HORRAD trial (n=432), the prescribed dose was either conventional schedule (70 Gy in 35 fractions) or hypofractionated schedule (57.76 Gy in 19 fractions of 3.04 Gy) (3). Radiotherapy group had not significantly improved overall survival compared with androgen deprivation therapy (ADT) alone (control group) (HR, 0.90; 95% CI, 0.70–1.14; P=0.40) in the HORRAD trial. In contrast, additional radiotherapy (15 months; 95% CI, 11.8–18.2) had significantly prolonged median time to prostate-specific antigen progression (crude HR, 0.78; 95% CI, 0.63–0.97; P=0.02) compared with ADT alone (12 months; 95% CI, 10.6–13.4). Differences in prostate radiotherapy regimens should be carefully considered while designing comparisons among this type of clinical trials. Overall, the optimum dose schedule and technique in the setting of additional radiotherapy to the primary prostate tumor for metastatic PCa are still uncertain.

Rationale for interventions for primary tumors in metastatic disease

The concept of the trial was based on the hypothesis that additional radiotherapy could improve survival in patients with newly diagnosed mPCa and that especially patients with low metastatic tumor lesions could be received the greater clinical benefit. Many of the host-derived stromal cells and immune cells, such as myofibroblasts, M2 macrophages (tumor-associated macrophages), regulatory T cells, and tumor-associated endothelial cells, have pro-tumoral roles in the tumor microenvironment (4-7). Similarly, the host systemic environment's contribution to tumor growth has been investigated well so far. Preclinical studies have demonstrated that initiation of distant disease as well as progression of existing metastases is largely dependent on substances released from the primary tumor into the circulating blood. McAllister *et al.* found that human breast carcinomas induced the systemically growth of other indolent cancer cells and micrometastases by incorporating bone-marrow cells into the stroma of distant tumors (8). To date, several RCTs have evaluated the clinical benefit from local control therapy of primary lesion in patients with metastatic cancers. However, evidence supporting the clear benefit of intervention for primary tumors in patients with metastatic disease is limited. In some of previous RCTs, intervention for primary tumors had not improved survival in patients with metastatic breast cancer (9) and metastatic small-cell lung cancer (10). A similar idea involving surgical removal of the primary lesion in patients with metastatic disease has also emerged. For examples, cytoreductive nephrectomy in metastatic renal cell carcinoma may be the most familiar concept for urologists. Although two large RCTs implemented in the era of cytokine therapy (interferon alpha and interleukin-2) confirmed cytoreductive nephrectomy had substantial improvements in survival (11,12), cytoreductive nephrectomy have not significantly improved progression-free survival compared with molecular target therapy alone in a recent RCT implemented in the era of molecular target therapy [Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques (CARMENA) trial] (13).

Concept of oligometastatic disease

The term "oligometastasis" was first coined in 1995 by Hellman *et al.* (14). Because of recent advancements in imaging technologies, oligometastatic sites can be detected in patients who were diagnosed with localized PCa in the past. Theses advancements include ^{99m}Technetium-methylene diphosphonate (^{99m}Tc-MDP) bone scan, ^{11}C-choline positron emission tomography/computed tomography (PET/CT), PET/magnetic resonance imaging (MRI), ^{18}fluorodihydrotestosterone PET, ^{68}Ga-labelled prostate-specific membrane antigen PET/CT, combined ultra-small superparamagnetic particles of iron oxide-enhanced and diffusion-weighted MRI, and ferumoxytol enhanced MRI (15-18). Oligometastatic disease is thought to be a heterogeneous disease entity with distinct malignant phenotypes, with different levels of aggressiveness. In a recent comprehensive review, several studies imply treatments for oligometastatic PCa, including cytoreductive prostatectomy, radiotherapy, and metastasis-directed intensive therapy, might to be potential therapy to improve survival and might be applied for selected patients for intensive treatment (19).

Evidence of cytoreductive prostatectomy for metastatic prostate cancer

Cytoreductive prostatectomy, in addition to radiotherapy, has received attention for treatment of mPCa. Although there have been no RCT, emerging evidence suggests that cytoreductive prostatectomy might be a potential therapy to provide a survival benefit in selected patients. A recent review article by Jaber *et al.* precisely described the rationale for cytoreductive prostatectomy, related oncological outcome and safety, and ongoing prospective trials (20). Most previous studies have demonstrated that cytoreductive prostatectomy has an acceptable safety profile regarding complications and perioperative mortalities. However, compared to prostatectomy for localized disease, cytoreductive prostatectomy for mPCa with oligometastasis is considered to need more sophisticated operative technic, with increased blood loss and transfusion rate during operation and increased length of hospital stay (21). In 2014, two large-scale population-based studies utilized the Surveillance, Epidemiology, and End Results data to compare survival between mPCa patients who were received cytoreductive prostatectomy or brachytherapy and mPCa patients without definitive therapy (22,23). Although an unavoidable potential bias was present due to the retrospective population-based nature of these studies, both multivariate competing risk regression analysis and propensity-score matched analysis showed improvements in cancer-specific death with cytoreductive prostatectomy for all M stages. Jaber *et al.* concluded that cytoreductive

prostatectomy should not be selected outside clinical trial settings because of the current lack of adequate evidence to support its selection (20). Another benefit of prostatectomy in patients with mPCa involves reduction of concurrent or future prostate-related symptoms, including bladder irritability, urinary retention, gross hematuria, and hydronephrosis. Approximately one third of patients with mPCa require subsequent intervention for complications related to local progression. Without any doubt, prostatectomy significantly reduces the risk of future complications. Based on this idea, local therapy would be appropriate, especially for patients with bulky prostate tumors who are likely to develop symptomatic primary disease.

Concluding remarks

Many questions regarding the clear benefit of prostate radiotherapy or cytoreductive prostatectomy for mPCa still remain unanswered. Better understanding of the biology that drives mPCa and high-level evidence obtained through clinical trials is absolutely needed. Currently, many ongoing clinical trials are investigating the potential role of multidisciplinary treatments for improved survival in mPCa patients. For instance, a randomized phase II trial (NCT01558427) is testing the benefit of metastasis-directed therapy combined with surgery or stereotactic body radiation therapy for oligometastatic recurrent disease after local therapy, compared to the benefit of active surveillance (24). The Testing Radical prostatectomy in men with prostate cancer and oligometastases to the bone (TRoMbone) RCT includes 50 patients with mPCa who are randomized to receive either standard-of-care involving ADT with or without docetaxel or receive standard-of-care plus cytoreductive prostatectomy with extended pelvic lymph node dissection (ISRCTN15704862). Summarizing results of the ongoing trials and acquiring actionable data will expedite evaluation of the feasibility of aggressive multimodal treatments and optimal treatment strategies for each individual.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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