Editorial Commentary

Prostate radiotherapy for metastatic hormone sensitive prostate cancer—myth or reality?

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Previously, local radiotherapy (RT) was only limited to palliate local symptoms, including bleeding or obstructive symptoms in metastatic prostate cancer patients. However, a population-based database and retrospective studies suggested that the local treatment of the prostate could improve survival in metastatic hormone-naïve prostate cancer with a small metastatic burden, 'oligometastatic' state (1-3). Recently two randomized trials demonstrated the efficacy of local RT to prostate in metastatic prostate cancer patients (4,5).

In STAMPEDE trial comparing hormonotherapy ± docetaxel with RT to prostate, 2,061 newly diagnosed metastatic prostate cancer patients were analyzed (4). Although overall survival (OS) was not improved with local RT (HR =0.92, 95% CI: 0.80–1.06; P=0.266), a significant improvement in failure-free survival (FFS) was observed with prostate RT compared to standard of care alone (HR =0.76, 95% CI: 0.68–0.84; P<00001). However, in subgroup analysis according to metastatic burden defined in CHAARTED study (6), an OS (HR =0.68, 95% CI: 0.52–0.90; P=0.007) and FFS (HR =0.59, 95% CI: 0.49–0.72; P<0.0001) benefit was observed in patients with a low metastatic burden. However, patients with a high metastatic burden did not benefit from radiotherapy in terms of OS and FFS. The authors concluded that RT to primary tumor should be an option for newly diagnosed metastatic prostate cancer patients with low metastatic burden.

In second randomized trial, HORRAD trial, 432 men with metastatic prostate cancer were randomly allocated androgen deprivation therapy either alone or with prostate RT (5). Addition of external RT to primary tumor did not significantly improve OS compared to androgen deprivation alone (HR =0.90, 95% CI: 0.70–1.14; P=0.4). However in subgroup analysis, in patients with less than 5 bone metastasis including 160 patients, prostate RT improved OS with borderline significance (HR =0.68, 95% CI: 0.42–1.10).

These two randomized studies addressed the importance of local RT to prostate in newly diagnosed metastatic prostate cancer with low metastatic burden. Although the definition of metastatic burden (high *vs.* low) is well-described in STAMPEDE study, HORRAD trial collected the number of bone metastasis in three subcategories (<5, 5–15 and >15). Thus, a meta-analysis is crucial to define the patient population that benefits from primary tumor RT. The STOPCAP meta-analysis (7) is a prospective framework adaptive meta-analysis including one ongoing PEACE-1 study and two completed STAMPEDE and HORRAD studies (4,5). The pooled results of 2,126 patients *de novo* metastatic prostate cancer did not demonstrate a significant improvement in OS (HR =0.92, 95% CI: 0.81–1.04; P=0.195) and progression-free survival (PFS) (HR =0.94, 95% CI: 0.84–1.05; P=0.238) with prostate RT. There was no significant effect of adding prostate RT to androgen deprivation treatment on OS by patient age, performance status, clinical T-stage and Gleason score. However, the effect of prostate RT on OS (HR =1.47, 95%

CI: 1.11–1.94; P=0.007), PFS (HR =1.32, 95% CI: 1.04–1.67; P=0.021), and FFS (HR =1.35, 95% CI: 1.10–1.66; P=0.004) was evident in patients with less than five bone metastasis, when stratification was made on number of bone metastasis (<5 *vs.* ≥5 metastases).

Although STOPCAP meta-analysis is important in demonstrating the effect of prostate RT on survival according to metastatic burden, there are some limitations. Most important limitation is the methods of metastasis detection with conventional imaging modalities, which has a limited value. Recent studies have demonstrated that the sensitivity and specificity of bone scintigraphy in detecting osseous metastases were 46–89% and 32–57%, respectively (8). However, several studies have demonstrated the benefits of ^{68}Ga-PSMA-PET/CT in identifying metastasis (9). Thus, staging with ^{68}Ga-PSMA-PET/CT is essential for appropriate staging. Furthermore, the RT doses to prostate delivered in STAMPEDE (either 36 Gy in 6 fractions or 55 Gy in 20 fractions) and HORRAD (70 Gy in 35 fractions or 57.76 Gy in 19 fractions) were significantly lower than suggested doses for high-risk prostate cancer patients (10). Therefore, studies with higher prostate irradiation doses may be more beneficial to demonstrate true effect of local RT.

Based on the findings of STOPCAP (7), primary prostate RT could be considered for newly diagnosed metastatic prostate cancer patients with less than five bone metastases. But further studies with better staging and higher local RT doses are needed to better define the benefit of prostate RT and also to delineate the clinical implementation of such treatment.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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