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EDITORIAL COMMENT

Retrospective evaluations of the treatment of the primary tumor in the setting of metastatic hormone sensitive prostate cancer (mHSPC) are prevalent in the recent literature. The majority of these reports have favored the addition of local therapy¹ and form the hypothesis generating support for recently completed and ongoing prospective randomized studies.^{2,3} Interestingly, in the present retrospective study, cancer-specific survival was not improved with local therapy. This is intriguing since the patients were subject to similar selection biases present in other retrospective reviews favoring local therapy. Information why the 35 patients who had surgery were selected for such is lacking, but a strong bias towards more favorable disease characteristics was evident. They had lower presenting PSA level, clinical T stage, radiographic N stage, lower Gleason score, and fewer number of bone metastases. Additionally, the median PSA nadir in the group that underwent surgery was 1.7 ± 6.1 ng/mL compared to 6.8 ± 17.9 ng/mL in the ADT alone group. Thus it is possible that some of these patients were selected based on their favorable response to ADT (30% received ADT prior to surgery). Since initial treatment response has been previously demonstrated as a predictor of survival,⁴ it is somewhat surprising that in spite of the favorable profile of the patients that underwent surgery there was no statistically significant difference in cancer-specific survival between groups. However, given the small numbers it is likely underpowered and prone to type II error. Nevertheless, it provides opportunity to examine the nuances of the literature evaluating local treatment in mHSPC.

Similar to this study, 2 recently reported randomized trials evaluating radiotherapy to the primary tumor in mHSPC were also negative for survival benefit in unselected patients.^{2,3} While the subgroup analysis of STAMPEDE Arm-H provides an encouraging signal of benefit from definitive treatment of the primary tumor with radiation in low-volume mHSPC, the generalizability of these results to contemporary practice is unclear. No patient received abiraterone in addition to ADT, and a minority (16%) received docetaxel. Quantification of early systemic treatment resistance was notably absent. Additionally, the radiation dose used was less than present standards and symptomatic local progression was substantial and no different between groups (42% control vs 44% radiotherapy).

Choice of initial systemic therapy and the patients' response, duration of response, initial and subsequent tumor profile will all be important to properly select patients' optimal treatment course, including the potential application of local therapy.⁵ We await the results of the PEACE1 study (NCT01957436)

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which will provide data regarding radiation to the primary with contemporary systemic therapy (abiraterone and docetaxel). Analysis of the Phase II study of best systemic therapy or best systemic therapy plus definitive treatment (NCT01751438) which has fully accrued, as well the similar Phase III study (NCT03678025) which is actively enrolling will also be forthcoming. In addition to providing the first prospective data regarding prostatectomy in the mHSPC setting, these data will also provide insight to guide future trial design to evaluate for maximal local therapy benefit. There are still many unknowns regarding treatment of the primary tumor in mHSPC and support of ongoing clinical trials is critical to provide answers.

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AUTHOR REPLY

For men with localized prostate cancer (CaP), radical prostatectomy (RP) as well as radiotherapy (RT) was associated with lower incidences of progression and metastases than was active monitoring.¹ Meanwhile, prospective trial showed these patients with a long life expectancy would benefit from surgical intervention with a mean gain of almost 3-year of life.² Unfortunately, when localized CaP progressed to incurable metastatic disease ancestral subclones and stromal micro-environment evolved dynamically in space and time following principles of selective evolution, underpinning important emergent features such as therapeutic resistance and clinical aggressivity. Recently, emerging evidence from retrospective series suggests that cytoreductive prostatectomy might be a potential therapy to provide a survival benefit in selected patients with metastatic CaP. More