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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

importantly, using CHARTED definition for low or high metastatic burden, STAMPEDE randomized controlled trial showed additional RT for primary tumor had improved 3-year overall survival compared with standard of care in a subgroup of patients with low metastatic burden.³ Consequently, we spontaneously hypothesized that men with oligometastatic prostate cancer should benefit from RP although potential therapeutic mechanism was different between RP and RT.

"In the world of surgical oncology; biology is King; selection of cases is Queen; the technical details of surgical procedures are princes. And the princesses frequently try to overthrow the powerful forces of the King and Queen." It seems plausible given this hypothesis that an intact primary tumor may continue to shed metastases. However, there may be other radiation-specific mechanisms such as immunomodulation or an interplay between radiation and androgen deprivation, which contribute to the observed survival benefit by RT. Meanwhile, definitions of oligometastatic disease vary by number and location of lesions, with no consistency in current literature or ongoing clinical trials. Despite the clues to risk provided in patients population with the metastatic hormone sensitive CaP, ambiguity remains in defining the extent of metastatic burden that constitutes "oligometastatic disease."

Before cytoreductive RP was recommended for the patients with newly diagnosed oligometastatic CaP some stumbling blocks should be moved away firstly. First, defining a metastatic volume threshold above which patients are unlikely to benefit from RP is still an important area of further study. Admittedly, in current risk-stratification models including J-CAPRA⁴ and Glass model,⁵ the number of skeletal metastases was not the overarching factor for prognosing progression and mortality. Second, the standard definitions of resectable localized tumor and regional metastatic lymph-nodes should be further refined, which should be employed as a guide for surgical procedure. As each of pelvic regions has its own associated challenges to evaluation and resection the volume and distribution of disease within

the pelvic cavity are consistently identified as an important prognostic factor for recurrence and survival. Third, PSA kinetics itself is an independent prognostic factor for metastatic CaP, and current data from published repositories have not yet elucidated the association between the responsibility to neoadjuvant androgen deprivation therapy and survival benefit of cytoreductive RP. The use of neoadjuvant treatment including hormonotherapy and chemotherapy in patients undergoing cytoreductive surgery has not been extensively studied.

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