Improved Survival With Local Treatment of Prostate Cancer in Men With Metastatic Disease: Look Before You Leap

**To the Editor:** In the recent report by Rusthoven et al that analyzed the overall survival (OS) outcomes for patients with metastatic prostate cancer (mPCa) treated with androgen deprivation therapy (ADT) alone versus prostate radiation therapy (RT) plus ADT, all data were derived from the National Cancer Data Base (NCDB) between 2004 and 2012. The authors found that prostate RT plus ADT is associated with significantly improved 5-year OS compared with ADT alone (49% vs 33%; hazard ratio [HR], 0.67; P < .001) after accounting for available covariates. We recently performed a comprehensive analysis of the impact of local treatment (LT; radical prostatectomy [20%] or RT [80%]) versus no LT (defined as ADT alone [69%], watchful waiting [22%], or external-beam RT not targeted to the prostate [9%]) in men with mPCa recorded in the NCDB between 2004 and 2012 and noted an OS benefit in patients treated with LT versus no LT (3-year OS, 69% vs 54%; HR, 0.60; P < .001) with no difference between radical prostatectomy and RT on OS. As such, Rusthoven et al corroborate these results. These findings highlight the growing and rapidly evolving paradigm for local treatment of mPCa, the mainstay of treatment of which has traditionally been ADT. However, some key areas in the analyses by Rusthoven et al need attention before the results of their study are generalized to the average patient with mPCa.

Perhaps most importantly, Rusthoven et al did not incorporate baseline risk factors in quantitatively estimating the survival benefit of RT plus ADT. As we have shown, the impact of LT on OS in patients with mPCa is governed by preoperative patient characteristics (age, Charlson comorbidity index), and we created a novel risk calculator that is based on these factors to quantify the baseline risk of overall mortality (as shown in the data supplement of our article). Of note, for patients with a predicted mortality of > 70%, LT did not significantly improve OS. Although Rusthoven et al performed a classification and regression tree analysis, the latter creates distinct prognostic groups based on OS but does not quantify risk of mortality or provide a cutoff that demarcates when a patient will cease to benefit from LT. Furthermore, although the end point was OS (as opposed to PCA-specific survival), the authors did not include two important covariates: comorbidity status and M stage. These variables were included in our risk calculator and were the strongest predictors of OS in our analyses. The lack of adjustment for these variables can significantly limit the generalizability and clinical utility of the classification and regression tree model as proposed by Rusthoven et al because these variables represent an intrinsic part of the clinical assessment of patients presenting with mPCa and may be critical determinants of survival outcomes.

Rusthoven et al also explored the effect of adding RT to ADT in treating patients with mPCa. Although a comparison of the effect of the addition of LT to the standard of care (ie, ADT) seems plausible, a significant proportion of patients with mPCa (31% in our analyses) may undergo watchful waiting for their disease or receive palliative RT for bony metastases. Why these patients were excluded in the study by Rusthoven et al is not entirely clear. Indeed, subgroup analyses would be useful in identifying which patients are likely to benefit the most from the addition of RT directed to the prostate and would increase the generalizability of the findings.

Finally, the effect of the site of metastases was not quantified, which represents a key limitation of the study design. Contrary to the authors’ claim, the NCDB does record site of metastases at diagnosis through the Collaborative Staging system derived from the American Joint Committee on Cancer, 6th (2004 to 2009) and 7th (2010 to 2016) editions. In our analyses we observed that the majority of men with mPCa harbor M1b stage, which indicates bony metastases. Our Cox proportional hazards model showed M1a stage to be associated with a significantly lower risk of mortality (HR, 0.67; P < .001) compared with M1b disease. Conversely, there was no significant difference in mortality between M1c (HR, 1.08; P = .3) and M1b stages. Furthermore, the CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial suggested that men with bony metastases might derive greater benefit from the addition of systemic chemotherapy to ADT (compared with other sites). Given these findings, it would have been interesting to study the survival benefit (if any) of RT plus ADT in patients with various sites of metastases or in those who receive chemotherapy with ADT. Such a study might provide further insight into the OS benefit of radiating the primary tumor site along with systemic ADT.

The real impact of primary tumor control in patients with mPCa will be verified in ongoing randomized (clinical trial information: NCT02454543) and nonrandomized (clinical trial information: NCT02458716, NCT02138721) prospective studies. Although observational studies seem to support the beneficial role of LT for prostate cancer in such settings, physicians must identify the optimal candidates for such an approach.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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