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European Association of Urology

Letter to the Editor

Reply to Ashwin Shinde, Richard Li, Arya Amini, and Scott Glaser's Letter to the Editor re: Liselotte M.S. Boevé, Maarten C.C.M. Hulshof, André N. Vis, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol 2019;75:410–8

Future Steps for Definitive Therapy in Metastatic Prostate Cancer: Lessons from the HORRAD Trial Until Randomised Controlled Trials Prove Different, Treat the Patient, Not His Imaging Results

We thank Dr. Glaser and his group for their view on our paper in *European Urology*. We hereby take the opportunity to address some issues.

The HORRAD trial was a prospective randomised phase 3 trial initiated more than a decade ago to investigate androgen deprivation therapy (ADT) with or without local radiotherapy of the prostate in patients with bone metastatic prostate cancer with a primary endpoint of overall survival [1]. We included patients with prostate-specific antigen (PSA) of >20 ng/ml, since at the time of trial commencement, patients with PSA below that level did not have a standard indication to perform a bone scan to rule out osseous metastases.

The rationale for the trial has been published previously [2]. The trial was not directed towards oligometastatic disease or metastases-directed therapy (MDT).

Univariate analysis in the HORRAD trial showed a significant difference for PSA-free survival (which Glaser et al did not appear to appreciate), but was negative for the primary endpoint of overall survival. It should be kept in mind that the set-up for treating the primary organ alongside ADT should be distinguished from the treatment of oligometastatic disease with MDT, in which ADT is not given as a standard.

The only prospective data from a randomised phase 2 trial reporting on the outcome for MDT come from the STOMP trial, which compared time to the start of ADT among patients with oligorecurrent prostate cancer opting for MDT or surveillance [3]. Beside a widely debated endpoint (ADT-free survival), the trial was small, with only 31 patients in each randomisation arm reached over a 3-yr period. Moreover, the statistical analyses presented used more or less unusual standards (a difference of 9 mo between MDT and surveillance was shown, with $p = 0.11$ and α and β of 0.20). Despite the finding that the indications for initiation of ADT were seemingly well defined (ie, symptomatic progression and radiological progression of disease), the paramount question in this trial is what triggers the treating clinician to perform new imaging. It might well be that radiological imaging was performed earlier in the surveillance arm because PSA levels were higher, or because PSA levels reached a certain psychological cutoff point earlier. Identification of non-oligometastatic disease by earlier clinician-initiated imaging may thus lead to the earlier initiation of ADT as compared to the MDT arm, in which the PSA levels were presumably lower. The initiation and timing of radiological imaging should therefore be defined properly in future trials, as this is directly associated with the time of ADT initiation. Unfortunately, more robust endpoints such as the time to castration-resistant disease or overall survival were not reported in this paper, so definite conclusions on the benefits of MDT in oligometastatic disease cannot be drawn. Nevertheless, the STOMP trial provides an important starting point for prospective phase 3 trials. For now, and as the first author of this seminal paper correctly states, MDT should only be given within well-performed clinical trials [4].

Conflicts of interest: The authors have nothing to disclose.

DOIs of original articles: https://doi.org/10.1016/j.eururo.2018.11.008, https://doi.org/10.1016/j.eururo.2018.09.008.

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November 1, 2018