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European Association of Urology

Letter to the Editor

Re: Fabian Lohaus, Klaus Zöphel, Steffen Löck, et al. Can Local Ablative Radiotherapy Revert Castration-resistant Prostate Cancer to an Earlier Stage of Disease? Eur Urol 2019;75:548–51

We read with interest the paper by Lohaus et al. [1] suggesting that local ablative radiotherapy can revert castration-resistant prostate cancer (CRPC) to an earlier stage of disease. While acknowledging the impressive prostate-specific antigen (PSA) response (73%) and long-term biochemical control (mean 17.9 mo) rates in this small and highly selected group of CRPC patients, we would like to highlight some concerns.

First, we have a minor comment regarding the title. CRPC is arguably a biological definition, and the authors do not indicate anywhere that the PCs of these patients become hormone-sensitive again at the cellular level. The clear PSA drop seen in the majority of patients could just as well correspond to a "debulking" effect.

Second, the authors claim that the two schedules used (3×10 Gy and 25×2 Gy) are "homogeneous". This is open to debate, since the equivalent dose in two fractions ($EQD_{2\ Gy}$) for the hypofractioned schedule is probably almost double that of the longer schedule, even when taking the uncertainty regarding the α/β value for PC into account.

Third, and most seriously, the authors do not report any imaging data, which are usually included in trials on systemic treatment in the CRPC setting [2]. The PSA progression definition (nadir + 2) is quite generous, especially for evaluation of a radiotherapy effect. Patients could very well progress on modern imaging before that point [3].

To provide some counterbalance to the data reported by Lohaus and colleagues, we would like to present our own prospective series of three patients with CRPC treated to four oligometastases in a prospective stereotactic ablative radiotherapy (SABR) dose-escalation trial (NCT03486431). Those patients were very similar to the men described in the paper: all patients had a controlled primary tumor (surgery and/or radiotherapy), rising PSA under androgen deprivation therapy (ADT) and one or two lesions on prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT), and continued ADT without adding second-line systemic treatment (Table 1). What is different is that, according to the study protocol, these patients received a second PSMA PET/CT scan at 6 mo after SABR. Interestingly, the results nicely illustrate some of the different possible outcomes for those patients: one is still controlled at 21-mo follow-up (both biochemically and radiologically), one patient has a slowly rising PSA (but below the progression threshold) with many new lesions on PSMA-PET/CT, while the last patient exhibited manifest biochemical and radiological progression after an initial PSA drop. Obviously, these very limited data prove absolutely nothing, apart perhaps from the real danger of underestimating progression in CRPC when monitoring PSA alone (which is moreover possibly not very relevant in this setting).

Table 1 – Patient and treatment characteristics

Parameter	Patient 1	Patient 2	Patient 3
Age at PET (yr)	76	62	73
PSA at PET (ng/ml)	2.5	2.6	3.0
Metastases treated (n)	1	1	2
Location	Lymph node	Lymph node	Bone and lymph node
Schedule	5×7.0 Gy	5×7.0 Gy	5×7.0 Gy
PSA nadir (ng/ml)	0.044	2.2	0.8
Follow-up (mo)	21	18	15
PSA progression	Not yet	Not yet	Yes
PET at 6 mo	CR at TL, no new lesions	CR at TL, several new lesions	CR at TL, several new lesions

PET = positron emission tomography; PSA = prostate-specific antigen; CR = complete response; TL = target lesion.

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We do applaud the effort by Lohaus et al, and taking their results together with those from a multicenter series reported by Triggiani et al. [4], we agree that there indeed appears to be some "signal" with SABR in CRPC. However, the fundamental question is whether delaying systemic treatment is a valuable goal in advanced PC, for which all the current literature suggests that life-prolonging systemic treatments are best not withheld until the last moment, but on the contrary should preferably be given as early as indicated [5].

Conflicts of interest: The authors have nothing to disclose.

References

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