



European Association of Urology



Letter to the Editor

Reply to Zhipeng Mai's Letter to the Editor re: Taimur T. Shah, Max Peters, David Eldred-Evans, et al. Early-Medium-Term Outcomes of Primary Focal Cryotherapy to Treat Nonmetastatic Clinically Significant Prostate Cancer from a Prospective Multicentre Registry. *Eur Urol* 2019;76:98–105

We would like to thank Dr. Mai for the pertinent points outlined regarding our manuscript [1] reporting outcomes from focal cryotherapy for prostate cancer and raises an important point on the selection criteria for focal therapy (FT) in general. Multiple consensus groups have broadly agreed that patients with low- to intermediate-risk disease are the best candidates for FT and we tend to agree with this criterion [2,3]. However, as our understanding of the benefits versus harms from radical treatments increases, we believe that this selection boundary will continue to be pushed further. Pragmatically, we allowed inclusion of patients with high-risk disease (early T3 disease), as these lesions can normally be included within the treatment field of focal cryotherapy. Dr Mai commented on an ablation zone of >1 cm surrounding the target lesion and our previous data have shown that this zone can be highly controlled to achieve adequate treatment margins [4].

Similarly, prostate-specific antigen (PSA) >20 ng/ml indicates either higher disease volume or a risk of nodal or micrometastatic disease, but in itself does not limit the efficacy of local treatment. Our data showed that although patients with high-risk disease (PSA >20 ng/ml or early T3 disease) had a higher rate of local recurrence needing further repeat FT (90% for intermediate-risk vs 68.4% for high-risk disease; $p = 0.14$), the overall rate of transition to radical or systemic therapy was not substantially different (85% for intermediate-risk vs 91% for high-risk disease; $p = 0.35$). An equal number of recurrences occurred-inside and outside the treatment field. This probably reflects the need to optimise treatment margins and the diagnostic pathway for preoperative detection of out-of-field lesions. Dr. Mai highlighted that a median of 25 transperineal biopsy cores were taken per patient. The number of cores was not

higher because a full 5-mm template prostate mapping (TPM) was not performed for all men; targeted cores with systematic sampling was carried out for a significant proportion. TPM may improve preoperative disease characterisation, but comes at the cost of higher rates of adverse events and overdetection of insignificant disease [5]. In the short to medium term there appears to be no harm from a staged FT protocol whereby new out-of-field lesions are detected during follow-up and treated in an expectant manner.

Dr. Mai also commented on the use of multimodal therapy with (neo)adjuvant ADT in high-risk disease. This is currently not standard practice in all with high-risk pathology, but we accept that ADT may improve oncological outcomes after FT, particularly as it may lead to reductions in tumour volume and neovasculature and can thus improve treatment margins and reduce the heat sink effect [6]. Our group is due to start recruitment to two parallel phase 2/3 randomised controlled trials called CHRONOS A and B (Comparative Health Research Outcomes of Novel Surgery in Prostate Cancer) comparing oncological outcomes for radical therapies versus FT and also FT versus FT with neoadjuvant hormonal therapy.

Finally, focal ablative modalities such as cryotherapy kill cells via coagulative necrosis, and thus cancer grade should theoretically not be an exclusion criterion. However, as evidence is currently lacking for this group and outside of a prospective trial, we would currently not advocate treatment with FT.

Conflicts of interest: Taimur T. Shah has received funding for conference attendance from Astellis, Ferring, and Galil Medical. Hashim U. Ahmed currently receives funding from the Wellcome Trust, Prostate Cancer UK, Sonacare, Trod Medical, and Sophiris Biocorp for trials in prostate cancer, and is a paid medical consultant for Sophiris Biocorp and Sonacare. Hashim U. Ahmed and Mani Arya are proctors for cryotherapy and are paid for training other surgeons in these procedures. Max Peters has nothing to disclose.

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References

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