

Has tailored, tissue-selective tumour ablation in men with prostate cancer come of age?

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There are two principal challenges that face the growing number of clinical investigators that are evaluating tissue-preserving therapies in men with prostate cancer.

The first is that every man's prostate is different. So different and so unique are the personal attributes of a man's prostate that it would, just like the iris or fingerprint, qualify as a unique identifier. It is just a few practical considerations that prevent it from doing so. This is a challenge that the clinician treating the liver, kidney or brain does not face – as these organs do not exhibit the between patient variability that we see in the prostate.

The second relates to within-patient (or within-prostate) differences. The nature of the tissue being treated will depend on which part of the prostate is being treated – peripheral, transition or central zone. Each of these zones will, in turn, be dependent on the age of the prostate, the extent of benign prostatic hyperplasia, exhibit calcification and or cysts and may or may not be infiltrated by acute and/or chronic inflammation.

These two sets of variability present considerable challenges to investigators that seek to selectively ablate a given zone of tissue, given that the nature of the target volume will be different in every man treated and exist in a context that is specific to the that man.

Add to this challenge the variability in prostate cancer tumour attributes - volume, location, heterogeneity (genetic, radiological and histological), degree of immune infiltrate and the extent of microscopic extension, we begin to get the picture (1).

The paper in this issue by van den Bos and colleagues describes a modern attempt to overcome these challenges and attempt and achieve personalize care to individuals, their prostate glands and their cancer (2).

The team used irreversible electroporation (IRE) to create a selective ablation zone around a given tumour volume, embracing a margin of 5-10mm. This method of ablation has certain attributes that lend itself to the task. It can be applied to any zone of the prostate. It is not limited by the size of the prostate. It can create lesions of variable volume. The treatment is quick and therefore not overly affected by

prostate gland swelling. Because the treatment uses an interstitial approach (needle based) the effectors of the treatment move with the prostate during respiration and changes in rectal fullness. These attributes mitigate most of the challenges generated by between-patient variability.

The authors describe the methods by which they manage tumour-specific differences. These important but rather technical constraints (to the non-expert) comprise: tumour-volume dependent variable needle load; individualized tissue impedance based energy adjustment; minimizing variability in needle to needle distance; application of a 10mm margin; and near term verification of tissue change with post-treatment MRI.

These conditions seem to have paid off. Although every patient underwent a treatment that was bespoke to both their prostate and their prostate cancer the results were most promising for this truly personalized sub-specialty of uro-oncology.

The treatment was safe. There were no high-grade adverse events reported in 63 men included in the analysis. The disease specific and generic quality of life was not compromised by the range of interventions administered except in relation to the sexual quality of life domain that was marginally affected - a median score of 66 prior to therapy diminished to 54 when measured again 6-months after treatment.

The authors managed to get a high proportion of men to undergo verification biopsy after treatment. From this they derived two oncological outcomes. These comprised freedom from clinically significant prostate cancer (high volume exclusive Gleason pattern 3 and/or any Gleason pattern 4 or 5) within and on the edge of field on the one hand and out of field on the other.

In patients who were free of any technical failure in relation to the administration of IRE and had a 10mm margin incorporated the results were very promising with the majority of the patients evaluated free of disease both within (97% [38/39 men]) and out of field (87% [34/39 men]).

Although the numbers of patients reported upon are relatively small, the overall results represent a welcome improvement on previously published phase one clinical trial data using IRE, probably as a result of better patient selection and optimization of energy delivery (3). The results, however, are reassuringly similar to previous case-series that used alternative energy sources but were predicated on an anatomical-based approach to tissue preservation (4). The tumour-based approach reported upon by van den Bos and colleagues is much more challenging as it exposes any subtle deficiencies in the base-line risk-stratification and imposes exacting constraints on the reliability of the energy source in creating irreversible cell kill where cell kill is intended.

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References

1. Linch M, Goh G, Hiley C, Shanmugabavan Y, McGranahan N, Rowan A, Wong YNS, King H, Furness A, Freeman A, Linares J, Akarca A, Herrero J, Rosenthal R, Harder N, Schmidt G, Wilson GA, Birkbak NJ, Mitter R, Dentre S, Cathcart P, Arya M, Johnston E, Scott R, Hung M, Emberton M, Attard G, Szallasi Z, Punwani S, Quezada SA, Marafioti T, Gerlinger M, Ahmed HU, Swanton C. Intratumoural evolutionary landscape of high-risk prostate cancer: the PROGENY study of genomic and immune parameters. *Ann Oncol*. 2017 Oct 1;28(10):2472-2480. doi: 10.1093/annonc/mdx355. PMID:28961847
2. van den Bos W, Scheltema MJ, Siriwardana AR, Kalsbeek AMF, Thompson JE, Ting F, Böhm M, Haynes AM, Shnier R, Delprado W, Stricker PD. Focal irreversible electroporation as primary treatment for localized prostate cancer. *BJUI* XXXX
3. Valerio M, Dickinson L, Ali A, Ramachandran N, Donaldson I, McCartan N, Freeman A, Ahmed HU, Emberton M. Nanoknife Electroporation Ablation Trial: A Prospective Development Study Investigating Focal Irreversible Electroporation for Localized Prostate Cancer. *J Urol*. 2017 Mar;197(3 Pt 1):647-654. doi: 10.1016/j.juro.2016.09.091. Epub 2016 Sep 30. PMID:27697580
4. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, Scott R, Allen C, Van der Meulen J, Emberton M. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol*. 2012 Jun;13(6):622-32. doi: 10.1016/S1470-2045(12)70121-3. Epub 2012 Apr 17. PMID:22512844