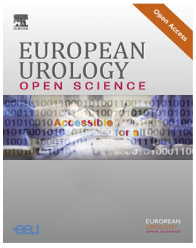
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Brief Correspondence

Applying Focal Therapy to Lesions Detected via Magnetic Resonance Imaging: Delivering Cancer Ablation Beyond the Visibility Phenomenon

Clement Orczyk [a,b,*], *Teresa Marsden* [a], *Francesco Giganti* [a,c], *Joseph M. Norris* [a], *Santosh Waigankar* [b], *Louise Dickinson* [c], *Shonit Punwani* [c], *Alex Kirkham* [c], *Alex Freeman* [d], *Aiman Haider* [d], *Caroline M. Moore* [a,b], *Arnauld Villers* [e], *Clare Allen* [c,†], *Mark Emberton* [a,b,†]

Article info

Article history:
Accepted January 17, 2025

Associate Editor:
M. Carmen Mir

Keywords:
Prostate cancer
Magnetic resonance imaging
Focal therapy
Treatment planning
Ablation
Perfusion imaging
Diffusion imaging
Histology
Margin
Segmentation

Abstract

The inclusion of imaging as a triage test in diagnostic guidelines for prostate cancer (PC) has introduced a visible target for guiding treatment allocation and disease management. Focal therapy (FT) is a promising approach with a low side-effect profile for treating magnetic resonance imaging (MRI)-visible PC within a limited framework of guideline recommendations or clinical trials. On the basis of accumulated clinical and research experience, we present a systematic approach to FT indications for ablation of visible targets that includes imaging findings, margin delineation, and energy selection. Confirmation of eligibility for FT is associated with the choice of energy source. We propose a 10-step framework that incorporates the contribution of all MRI sequences, the cancer growth pattern within the zonal anatomy to establish a margin around the MRI-visible lesion, safeguards for critical anatomic structures, and guidance for energy selection on the basis of specific properties. We discuss the key principles underlying this process. The aim of this methodology is to standardise FT interventions for MRI-visible PC and contribute to the development of a reproducible, stable treatment protocol. Quality control of the ablation procedure is crucial for broadening access to this technique beyond the confines of current regulatory pathways.

Patient summary: We propose a method for using results from magnetic resonance imaging (MRI) scans to guide targeted treatment of visible prostate cancer lesions. This will help to ensure accurate coverage and eradication of all of the cancer while minimising side effects.

The prostate cancer (PC) landscape is evolving toward a dominant MRI-visible phenotype since the adoption of multiparametric MRI (mpMRI) as the test for biopsy indication and guidance in most guidelines. Men with no visible

† These authors share senior authorship.

https://doi.org/10.1016/j.euros.2025.01.010

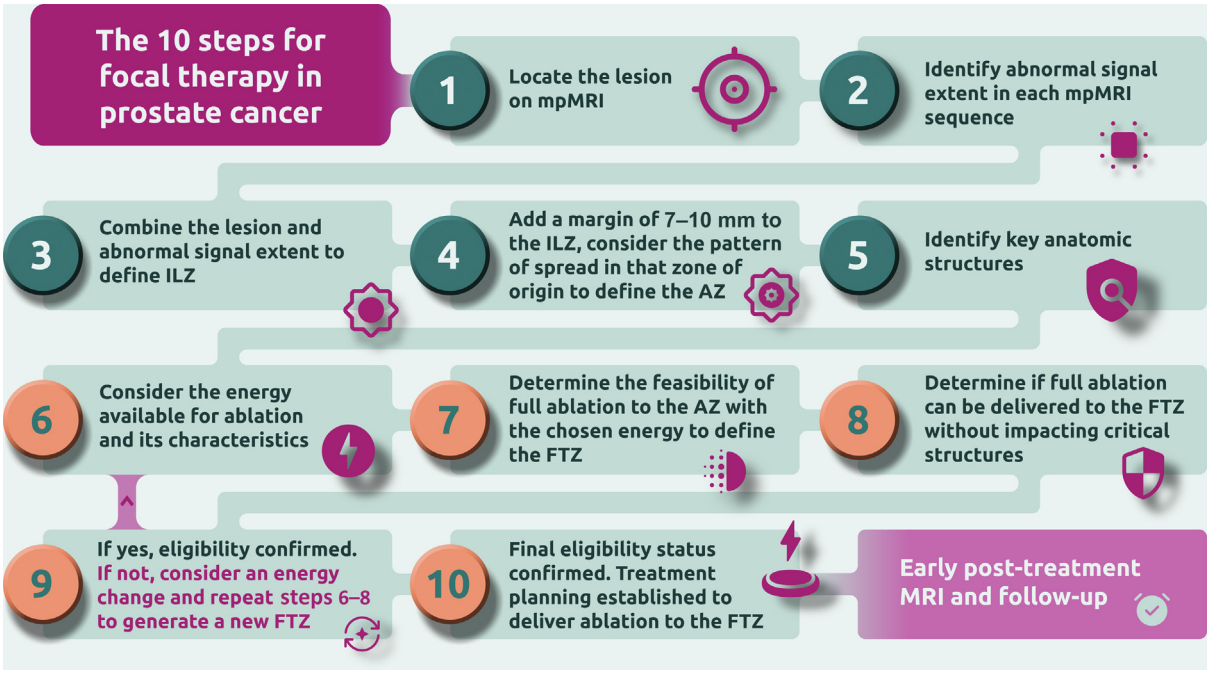


Fig. 1 – Flowchart of the 10 steps for planning focal ablation of prostate cancer detected via multiparametric magnetic resonance imaging (mpMRI). AZ = ablation zone; FTZ = focal treatment zone; ILZ = imaging lesion zone.

tumour on MRI and no other risk factors (eg, high prostate-specific antigen density) often avoid prostate biopsy. The focal therapy (FT) concept is also shifting to nearly exclusively ablation of discrete tumours visualised on imaging. The risk of progression associated with an MRI-visible tumour [1,2] seems to offer an appropriate benefit/risk ratio for any treatment. Focal ablative therapy is now at the point at which thousands of patients in clinical trials or prospective registries have been treated with a number of different energy sources, and there is much agreement on who best to treat and how to treat them [3]. FT has reached some stability in terms of indications and delivery.

The major findings from initial studies on FT were the ability to retain erectile and continence functions by preserving one side of the prostate (at least one neurovascular bundle) and avoiding disruption of the pelvic anatomy while achieving some oncological control [4].

Here we discuss our experience and relevant results from registry data and formal clinical studies. We look at the role of pathology correlation and image analysis in planning complete ablation of a cancer focus associated with a lesion detected via mpMRI, encompassing both the MRI-visible and nonvisible parts of a cancerous tumour. We describe the interplay between the location of PC, the tumour margin and its direction, the choice of energy for FT, and preservation of critical structures.

It is now well established that mpMRI consistently underestimates the actual volume and extent of cancer, and a predicted margin should be applied in all cases [5]. The first set of characteristics to consider are the signal attributes of the proven cancer visualised on imaging. Imaging provides exquisite details regarding PC location, the zone of origin of the cancer, and its extent through different MRI sequences. The visibility of cancer on MRI identifies a tumour within its microenvironment. It has been demonstrated that each sequence captures a different aspect of the volume of the tumour, and each will have spatial implications for treatment [5,6]. Combined with the spatial heterogeneity of a PC focus at the molecular level, it is critical to encompass the whole tumour with FT [7].

The treatment questions posed for imaging for FT planning, delivery, and follow-up differ from the questions for the detection setting. Owing to the heterogeneity of PC, all the sequences used in planning a target for ablation provide relevant and critical information. No systematic imaging sequence drives the process, unlike the diagnostic setting, where diffusion sequences are the main drivers for the Prostate Imaging-Reporting and Data System.

Here we propose a systematic method for overcoming this characteristic of PC on imaging. The steps involved in creating an imaging-based target rely on visualisation of previous imaging on a dedicated platform and the use of prior radiology reports and histology data for correlation, as summarised in the flowchart in Fig. 1.

1. Locate the lesion on mpMRI within the zonal anatomy (peripheral zone [PZ], transition zone, anterior fibromuscular stroma) and the relationship to internal landmarks (apex, ejaculatory ducts, urethra, tip of the anterior horn of the PZ).
2. Identify the extent of the abnormal signal in each sequence separately. Windowing and use of different planes are critical. On the dynamic contrast enhancement sequence, the time point corresponding to the maximum extent must be selected. In some sequences with less sharp boundaries, reference to another diag-

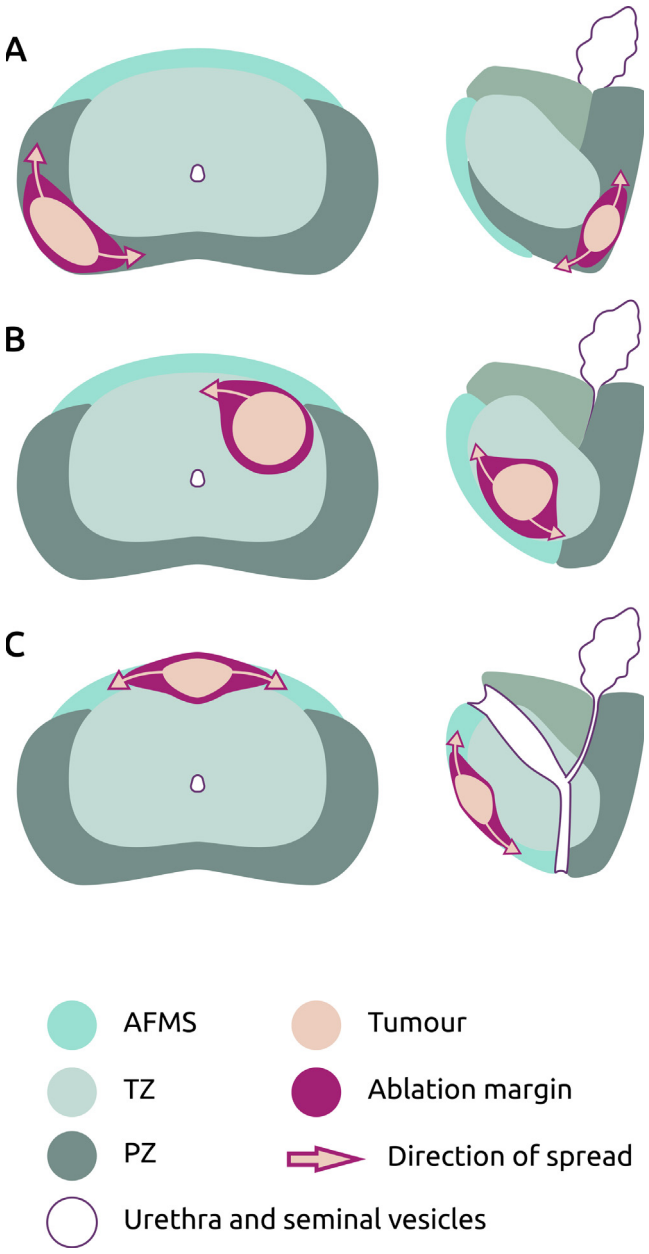


Fig. 2 – Direction of the pattern of growth of prostate cancer according to the zonal anatomy. AFMS = anterior fibromuscular stroma; PZ = peripheral zone; TZ = transition zone.

nostic sequence can be made before allocation of an additional significant volume as cancerous (eg, nodules in benign prostatic hyperplasia or diffuse signals in the PZ).

3. Combine the sequences in space to build a volume to encompass all abnormal MRI signals associated with cancer to establish the imaging lesion zone (ILZ).
4. Apply a margin of 7–10 mm within the gland, considering the pattern of spread of the cancer according to the zonal anatomy, as illustrated in Fig. 2 [8]. Each zone of origin of cancer exhibits a specific spatial pattern of growth (Fig. 2) [9,10]. This establishes the ablation zone (AZ).
5. Identify key pelvic anatomic structures:

a.

To avoid complications, identify the rectal wall, pubic symphysis, and bladder neck.

b.

To preserve function, identify the membranous urethra, striated sphincter, and neurovascular bundles.

6. Consider the energy available for ablation and its characteristics, including:

a.

The route for energy delivery (eg, transperineal needle-based, transrectal, or transurethral);

b.

The mechanism of ablation (thermal vs nonthermal) to induce cancer cell death; and

c.

The expected extent of tissue that will be partly damaged beyond the AZ; this represents a zone of transition from fully ablated tissue to partly damaged tissue to intact tissue.

7. Determine the technical feasibility of delivery of full ablation of the AZ according to step 4 using the chosen energy to establish the focal treatment zone (FTZ). Parameters to consider are:

a.

Characteristics intrinsic to the energy source, such as energy absorption by tissue, the need for overlap, and the number of probes.

b.

Characteristics extrinsic to the energy source, such as anatomic variations (calcification and hyperechoic material [corpora amylacea]), vessels (heatsink effects), cysts, and tumour access.

When planning the FTZ, the error inherent to delivery of the energy as a procedure and potential challenges in imaging registration must be considered.

8. Determine if energy can be delivered to the FTZ from step 7 without impacting the critical structures identified in step 5.
9. If the energy can be delivered, eligibility is confirmed, If not, consider a change in energy and repeat steps 6–8 to generate a new FTZ.
10. Final eligibility status for FT is confirmed or not. Treatment planning is established to deliver FT to the FTZ.

The aim of these 10 steps is to facilitate planning of FT for complete ablation of cancer associated with an mpMRI-visible lesion according to the energy modality chosen. Representative examples for HIFU and cryotherapy are shown in Figs. 3 and 4. An additional imaging modality can be added, with a similar cumulative approach used to enrich the ILZ.

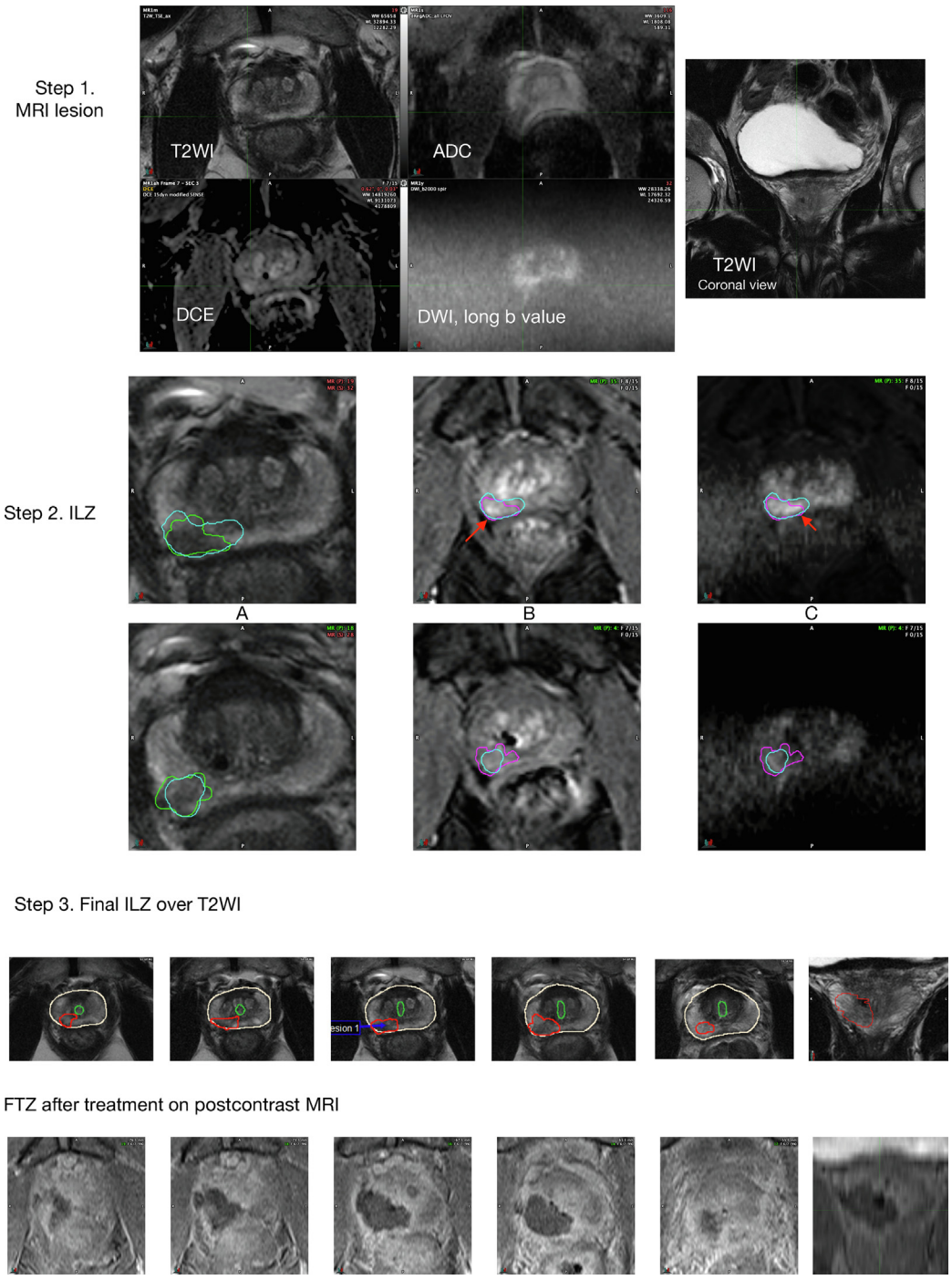


Fig. 3 – Planning and delivery of focal therapy: steps for generating the image lesion zone. Step 1. Localisation of the tumour using axial views of2 T2-weighted imaging (T2WI), dynamic contrast enhancement (DCE), an apparent diffusion coefficient (ADC) map, diffusion- weighted images (DWI) with long b values and coronal views of T2WI. Step 2. Imaging of the lesion at two different levels of the gland showing a segmented MRI lesion associated with a focus of grade group 2 cancer; the contours are overlaid after rigid image registration. (A) Contours for T2WI (green) and a long b value (blue). (B) DCE sequence contours for a DCE-visible lesion (purple) and imaging with a long b value (blue). (C) Diffusion-weighted imaging (DWI) with a long b value: DCE (purple) and long b (blue) contours. Red arrows highlight the maximum signal intensity on DCE and DWI. Note the spatial difference between sequences in depicting a component of the tumour. Step 3. ILZ as a combination of the tumour signal in different sequences. The combination is the total extent of the union of all contours from the different sequences, encompassing the visible signal in each sequence, including overlapping areas as well as sequence-specific imaging signals. The last row shows early MRI after focal high-intensity focused ultrasound (DCE sequence) demonstrating necrosis of the focal treatment zone (ILZ + margin) on axial and coronal views. FTZ = focal treatment zone; ILZ = imaging lesion zone; MRI = magnetic resonance imaging.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Those steps establish a margin around the MRI-visible cancer on different mpMRI sequences in relation to the zone of origin of the cancer and to the sharpness of the transition between treated and untreated tissue specific to an energy modality. The quality of the mpMRI influences the segmentation process, with the latest diagnostic imaging techniques probably serving as the standard reference [11]. Delivery of the treatment plan remains the ultimate goal

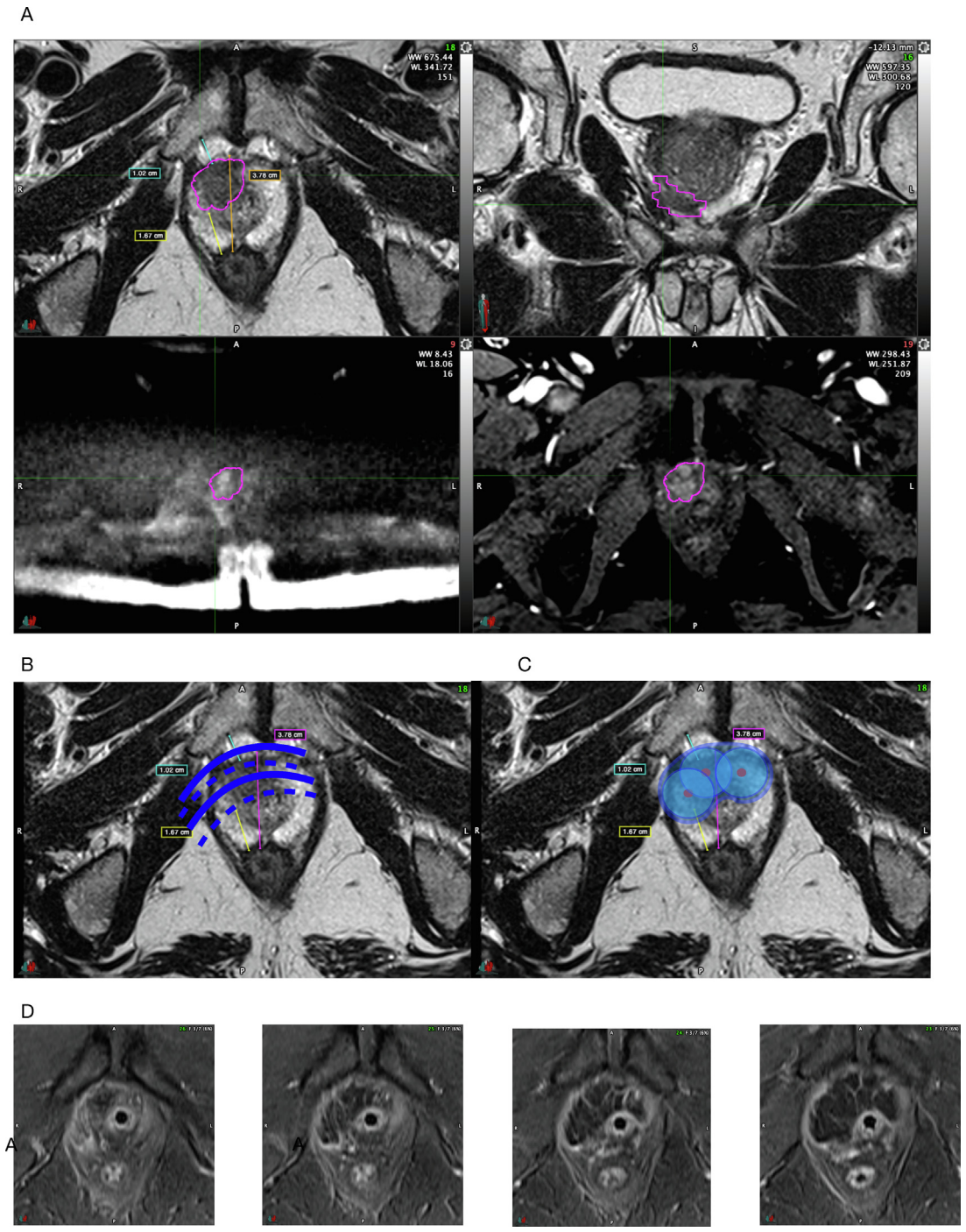


Fig. 4 – Choice of energy according to the location of the mpMRI-identified cancer focus. (A) Right anterior grade group 2 cancer focus associated with a Likert 4/5 lesion on axial T2WI, coronal T2WI, DWI with a long b value, and DCE imaging forming the ILZ (purple). Distances are measured in the axial plane from the most anterior component of the tumour (ILZ) to the pubic symphysis (light blue) and the rectal wall (orange). The distance from the posterior component of the ILZ to the rectal wall is shown in yellow. (B) Illustration of steps 6, 7, and 9 and simulation of the HIFU layout (blue lines). As described in step 7a, ultrasound absorption that reaches the most anterior component and through the urethra will lead to non-eligibility for focal HIFU. (C) Illustration of steps 6, 7, 8, and 10; step 6 simulation of the treatment plan for focal cryotherapy (step 7, 3 probes), with the different isotherms and iceball. In step 8, the pubic symphysis and rectum are at a significant distance from the simulated FTZ, so focal cryotherapy is feasible as a focal therapy option (step 9). (D) Early MRI at 1 wk after focal cryotherapy according to the plan established in step 10. Necrosis is evident as an non-enhancing area on the DCE sequence. DCE = dynamic contrast enhancement; DWI = diffusion-weighted imaging; FTZ = focal treatment zone; HIFU = high-intensity focused ultrasound; ILZ= imaging lesion zone; mpMRI = multiparametric magnetic resonance imaging; T2WI = T2-weighted imaging.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the operator, most likely under ultrasound guidance. Some additional residual error might be introduced by the use of a fusion/image registration platform [12]. Intraprocedural changes might need to be applied given the modifications that can occur to the gland during the procedure [13]. Use of the energy is directly related to the operator experience and this variable is likely to evolve with the learning curve. Early post-treatment MRI (3–14 d) with postcontrast sequences allows quality control of the plan delivered and provides a follow-up reference for assessing the margin

[14]. Establishing an AZ by applying an appropriate margin around the MRI signal abnormality should reduce "near-field" recurrence. One randomised controlled trial supports focal ablation with an appropriate margin versus systematic extended hemiablation [15].

We believe that these technical developments will refine the way in which FT is delivered as a stable procedure and will have an impact on oncological outcomes. The European Association of Urology guidelines recommend that focal ablation be performed in either a prospective registry or prospective trial setting, reflecting the need for quality control and measurement of outcomes. Structured follow-up with imaging is instrumental in determining the effectiveness of treatment delivered to MRI-visible disease, which is currently the dominant phenotype of PC [16].

Author contributions: Clement Orczyk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Orczyk, Allen, Emberton.
Acquisition of data: Orczyk, Marsden, Norris.
Analysis and interpretation of data: Orczyk, Marsden, Norris.
Drafting of the manuscript: Orczyk, Marsden, Norris.
Critical revision of the manuscript for important intellectual content: Villers, Moore.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: Giganti, Dickinson, Waigankar.
Supervision: Allen, Emberton, Punwani, Freeman, Haider, Kirkham.
Other: None.

Financial disclosures: Clement Orczyk certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Mark Emberton reports a consultancy role for Sonacare Medical, Angiodynamics, NINA Medical, Profound Medical, Exact Imaging, Minomic Medical, and Proteomix; and research funding from the Medical Research Council (MRC)/Cancer Research UK comprising £8 million of in-kind industry contributions managed via the MRC Industry Collaboration Agreement process. Clement Orczyk reports honoraria and travel/accommodation support from Sonablate and Varian. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

References

[1] Norris JM, Simpson BS, Parry MA, et al. Genetic landscape of prostate cancer conspicuity on multiparametric magnetic resonance imaging: a systematic review and bioinformatic analysis. Eur Urol Open Sci 2020;20:37–47. https://doi.org/10.1016/j.euros.2020.06.006.
[2] Wibmer AG, Lefkowitz RA, Lakhman Y, et al. MRI-detectability of clinically significant prostate cancer relates to oncologic outcomes after prostatectomy. Clin Genitourin Cancer 2022;20:319–25. https://doi.org/10.1016/j.clgc.2022.04.001.
[3] Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? Eur Urol 2022;81:5–33. https://doi.org/10.1016/j.eururo.2021.08.005.
[4] Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011;185:1246–54. https://doi.org/10.1016/j.juro.2010.11.079.
[5] Le Nobin J, Orczyk C, Deng FM, et al. Prostate tumour volumes: evaluation of the agreement between magnetic resonance imaging and histology using novel co-registration software. BJU Int 2014;114:E105–12. https://doi.org/10.1111/bju.12750.
[6] Cornud F, Khoury G, Bouazza N, et al. Tumor target volume for focal therapy of prostate cancer—does multiparametric magnetic resonance imaging allow for a reliable estimation? J Urol 2014;191:1272–9. https://doi.org/10.1016/j.juro.2013.12.006.
[7] Berglund E, Maaskola J, Schultz N, et al. Spatial maps of prostate cancer transcriptomes reveal an unexplored landscape of heterogeneity. Nat Commun 2018;9:2419. https://doi.org/10.1038/s41467-018-04724-5.
[8] Le Nobin J, Rosenkrantz AB, Villers A, et al. Image guided focal therapy of MRI-visible prostate cancer: defining a 3D treatment margin based on MRI-histology co-registration analysis. J Urol 2015;194:364–70. https://doi.org/10.1016/j.juro.2015.02.080.
[9] McNeal JE, Haillot O. Patterns of spread of adenocarcinoma in the prostate as related to cancer volume. Prostate 2001;49:48–57.
[10] Bouyé S, Potiron E, Puech P, Leroy X, Lemaitre L, Villers A. Transition zone and anterior stromal prostate cancers: Zone of origin and intraprostatic patterns of spread at histopathology. Prostate 2009;69:105–13. https://doi.org/10.1002/pros.20859.
[11] Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V. Prostate Imaging Quality (PI-QUAL): a new quality control scoring system for multiparametric magnetic resonance imaging of the prostate from the PRECISION trial. Eur Urol Oncol 2020;3:615–9. https://doi.org/10.1016/j.euo.2020.06.007.
[12] Bonmati E, Hu Y, Villarini B, et al. Technical note: error metrics for estimating the accuracy of needle/instrument placement during transperineal magnetic resonance/ultrasound-guided prostate interventions. Med Phys 2018;45:1408–14. https://doi.org/10.1002/mp.12814.
[13] Shoji S, Uchida T, Nakamoto M, et al. Prostate swelling and shift during high intensity focused ultrasound: implication for targeted focal therapy. J Urol 2013;190:1224–32. https://doi.org/10.1016/j.juro.2013.03.116.
[14] Orczyk C, Rosenkrantz AB, Mikheev A, et al. 3D registration of mpMRI for assessment of prostate cancer focal therapy. Acad Radiol 2017;24:1544–55. https://doi.org/10.1016/j.acra.2017.06.010.
[15] Zhang K, Teoh J, Laguna P, et al. Effect of focal vs extended irreversible electroporation for the ablation of localized low- or intermediate-risk prostate cancer on early oncological control: a randomized clinical trial. JAMA Surg 2023;158:343–9. https://doi.org/10.1001/jamasurg.2022.7516.
[16] Giganti F, Dickinson L, Orczyk C, et al. Prostate Imaging after Focal Ablation (PI-FAB): a proposal for a scoring system for multiparametric MRI of the prostate after focal therapy. Eur Urol Oncol 2023;6:629–34. https://doi.org/10.1016/j.euo.2023.04.007.

[a] *Division of Surgery and Interventional Science University College London London UK*
[b] *Department of Urology University College London Hospitals NHS Foundation Trust London UK*
[c] *Department of Radiology University College London Hospitals NHS Foundation Trust London UK*
[d] *Department of Pathology University College London Hospitals NHS Foundation Trust London UK*
[e] *Department of Urology Centre Hospitalier Universitaire de Lille Lille France*

* Corresponding author. Division of Surgery and Interventional Science, University College London, Charles Bell House, 43–45 Foley Street, London W1W 7TS, UK.
E-mail address: c.orczyk@ucl.ac.uk (C. Orczyk).