Focal therapies in prostate cancer

BY JONATHAN NOËL AND CHRISTOPHER OGDEN

The standard of care in the management of prostate cancer has, to date, always been to treat the whole gland. This has ranged from surveillance, surgical excision / prostatectomy or external beam radiotherapy / whole gland brachytherapy. With the evolution of MRI for the prostate and level 1 evidence revealing that it has a high sensitivity and negative predictive value for clinically significant prostate cancer [1], lesions identified are confidently targeted with focal therapy (FT). FT has the benefit of optimising outcomes of urinary continence, erections and bladder / bowel function post prostate cancer treatment. This article will go into the FT options available on the urology market, and to some extent the senior author's experience with focal therapy following a background of experience in open and now robotic assisted retropubic and perineal prostatectomy.

For small renal masses FT, such as cryoablation and radiofrequency ablation, holds a similar advantage to avoiding the risks of surgical excision. In most instances, a renal biopsy is necessary to define the target lesion to guide appropriate therapy. The same is true for prostate cancer with regards to lesions on imaging. Satellite tumours are not able to be appreciated on MRI, but their clinical significance over the index lesion remains to be determined. Systematic biopsies are therefore recommended to stage the disease fully, rather than targeted biopsies only as per a multicentre international panel [2]. This takes us into patient selection for FT.

FT is an option for patients who have undergone a multi-parametric MRI (mpMRI), systematic prostate biopsies revealing mainly small volume low risk (Gleason Score 3+3) lesions and a 10-year life expectancy. For this group, active surveillance (AS) is the standard of care followed by whole gland treatment. Intermediate risk (Gleason Score 3+4) lesions treated with FT, where whole gland treatment is the alternative, must be scrutinised as long-term follow-up studies mature. So far, a randomised controlled trial on photodynamic therapy [3] has shown an advantage over AS, and the urology community eagerly awaits further trials on other FT techniques.

FT techniques

Photodynamic therapy

This is the only technique with level 1b evidence showing reduced rates of positive prostate biopsies on follow-up, when compared to groups undergoing AS. This technique is the administration of padeliporfin intravenously, which when activated by laser light intraprostatically (753 nm) allows oxygen free radicals to form and creates a thromboembolic event to targeted areas.

High-intensity focused ultrasound

HIFU, as the name implies uses non-ionising ultrasound beams that are directed and concentrated to a focal point creating high temperatures (>60 degrees) to cause coagulative necrosis and internal cavitation. This is delivered transurethrally or transrectally. A systematic review found overall disease specific survival was 100%, continence was 100% but potency was preserved in 88.6% [4].

Cryotherapy

This involves the form of energy to ablate tissues by creating a cold environment. Cryoneedles are inserted into the selected area under ultrasound guidance, in a pattern to create an ice ball effect with resultant cellular membrane disruption and vascular changes. Published one-year incontinence rates were <1% but potency rates ranged from 0-40%, hence close to radical surgical treatment. Fistula formation is a risk factor with this technique, at <0.5% [5].

Laser therapy

This approach includes direct thermal ablation to the prostate area via MRI guidance. Fibres are inserted into the prostate directly. Pad-free continence and erectile preservation was reported as 100% in case series evaluations.

Focal brachytherapy

This whole gland use of brachytherapy in prostate cancer is well established. Radioactive permanent implantation of seeds into the prostate is standard (unless in the case of high-dose brachytherapy where seeds are temporarily placed). Focal areas receive these seeds. In series evaluating this technique, no secondary local treatment was required. Pad-free continence was 95.2% but potency was not available [4].

Radiofrequency ablation and irreversible electroporation

The former is another thermal procedure which uses alternative current via needle infiltration, however studies on its functional and oncological outcomes are limited. Irreversible electroporation (IRE) delivers low energy but high voltage current to the target area of the prostate. In case series of IRE, pad-free continence was 100% and erections were maintained in 95%.

Discussion

It has been shown above that these focal therapy technologies have the advantage of maintaining potency and continence but long-term data on the oncological outcome is the one point of contention among urologists. There are stage 2b studies on HIFU, brachytherapy, cryotherapy and photodynamic therapy, with the longest projected follow-up thus far being in the well-established brachytherapy technique (Clinical Trial NCT02391051 Focal Brachytherapy in Patients with Selected Low-risk Prostate Cancer - A Phase-II-trial).

FT in prostate cancer can range from ablating the lesions itself, to a quadrant, hemigland or contralateral neurovascular sparing. The range of ablation delivery does not bode well for international consensus to recommend one over the other outside of an experimental trial. Comparative randomised controlled trials to whole gland treatment would settle the discussion as proposed by Valerio et al. [3] in his systematic review. The selection criteria for FT may be its weakness as low-risk prostate cancer that otherwise could be managed under AS protocol equates to FT being seen as overtreatment. On the flip side, studies comparing AS show the superiority of FT in regards to histopathological, tumour stage and / or PSA progression and as follow-up matures and protocols align, the arguments against FT will weaken.

The multifocality of prostate cancer has been the challenge for urologists and radiologists, in that whether MRI with associated targeted biopsies is enough to pick up all significant cancer in the gland. It is still

therefore recommended that to achieve accurate and full staging, then additional systematic biopsies should be undertaken [6].

Patients who have undergone FT are followed up but (unlike AS) MRI and targeted biopsies are a challenge to interpret and execute. Disease recurrence must be agreed if triggering points are to be set on secondary treatments in the form of repeat FT or whole gland treatment. A Delphi consensus project [7] was a positive step towards pooling international standards for follow-up and we look forward to similar projects ahead.

Conclusion

It is challenging to compare focal therapy modalities to standard of care whole gland treatment or indeed AS. The variability in studies with regards to cancer risk stratification, ablative protocols, follow-up and management of outcomes means that randomised controlled trials are a necessity. To make recommendations on the backdrop of trial settings only is not our aim. However, when the above are addressed, the authors concur that the wider urological community would soon find this a most welcome arrow in the quiver of prostate cancer management.

References

1. Rhudd A, McDonald J, Emberton M, Kasivisvanathan V. The role of the multiparametric MRI in the diagnosis of prostate cancer in biopsy-naive men. *Curr Opin Urol* 2017;**27(5)**:488-94.
2. Scheltema MJ, Tay KJ, Postema AW, et al. Utilization of multiparametric prostate magnetic resonance imaging in clinical practice and focal therapy: report from a Delphi consensus project. *World J Urol* 2017;**35**:695-701.
3. Azzouzi A-R, Vincendeau S, Barret S, et al. Padeliporfin vascular targeted photodynamic therapy versus active surveillance: a randomised clinical trial in men with low-risk prostate cancer. *Lancet Oncol* 2017;**18**:181-91.
4. Valerio M, Cerantola Y, Eggener SE, et al. New and established technology in focal ablation of the prostate: a systematic review. *Eur Urol* 2016;**71**:17-34
5. van der Poel HG, van den Bergh RCN, Briers E, et al. Focal therapy in primary localised prostate cancer: the European Association of Urology Position in 2018. *European Urology* 2018;**74(1)**:84-91.
6. Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. *Eur Urol* 2015;**67**:569-76.
7. Muller BG, van den Bos W, Brausi M, et al. Follow-up modalities in focal therapy for prostate cancer: results from a Delphi consensus project. *World J Urol* 2015;**33**:1503-9.

TAKE HOME MESSAGE

- Focal therapy is under trial for prostate cancer and shows promise as a treatment option for low-risk and intermediate-risk patients.
- Long-term oncological outcome data is limited, but in time results should be available. Consensus on follow-up post FT should be available before wider adoption.
- The variable risks of post FT salvage whole gland treatment options should be openly discussed with patients.

AUTHORS

Jonathan Noël,

Specialist Registrar, The Royal Marsden NHS Foundation Trust, London, UK.

E: dr.jnoel@gmail.com

Twitter: @UroNoel

Christopher Ogden,

Consultant Urological Surgeon, The Royal Marsden NHS Foundation Trust, London, UK.

Declaration of competing interests:
None declared.