High-intensity focused ultrasound focal therapy for prostate cancer

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Focal therapy for prostate cancer delivered with high-intensity focused ultrasound offers benefits such as fewer side-effects than some other treatments. Ongoing trials will help inform how the therapy can be best used but in the meantime the authors argue for increased availability for suitable men.

Prostate cancer presents a broad spectrum of risk to men diagnosed with the disease. Consequently, a wide range of treatment strategies are needed so that the risks are commensurate with the benefits. Active surveillance is preferred for low-risk disease. Physical side-effects are delayed, and misclassification and progression of disease are detected through prostate specific antigen (PSA), MRI and re-biopsy tests, leading to treatment in some cases. Radical therapy is ideal for disease that, although localised, appears to present a high risk of progression or death if the patient is not treated.1

Focal therapy (also referred to as partial ablation) has emerged in the last 10 years as a middle ground where treatment and eradication of disease is possible in suitable cases, but without the burden of side-effects and complications seen with whole-gland therapies. Focal therapy can be delivered with high-intensity focused ultrasound (HIFU), cryotherapy, irreversible electroporation and other novel devices.2

Sonablate HIFU is one of the main treatment modalities used by urologists performing focal therapy in the UK (see Figure 1). At the moment, the Ablatherm Focal One system is not in use in the UK. The HIFU device has a probe that consists of two concave ultrasound probes that can both image and focus high power ultrasound to a 3cm or 4cm focal point. The probe sits in the rectum, which is protected by a cooling water balloon. While under a general anaesthetic the patient and probe are in a fixed position, the HIFU probe is moved precisely by the system, targeting all the areas planned for treatment by the surgeon. Real-time image feedback allows adjustment of the power by the surgeon, and patients can go home the same day of the procedure with a catheter for five to seven days.

Why focal therapy? Why not radical therapy?
This is the crux of many heated discussions among often polarised groups of clinicians. Focal therapy in treating other solid organ cancers has been well established over the last 20 years. Breast cancer is now mostly treated with wide local excision, resulting in similar overall survival with significantly improved postoperative morbidity compared with mastectomy.3 However, tissue-sparing techniques have been difficult to develop within the prostate cancer field due to the historic difficulty in accurately localising the regions of the gland affected by the disease.

Contemporary diagnostic and staging processes attempt to both accurately locate cancer within an otherwise healthy prostate gland and
risk-classify such disease. The widely covered developments in multiparametric MRI (mpMRI) have dramatically improved this process, and mapping biopsy techniques can overcome any uncertainties on imaging. It is possible for clinicians to confidently identify a group of up to 51% of cases that would be eligible for focal therapy, when the alternative would be to undergo radical treatment. Such management may be able to eradicate the clinically significant disease and deliver a treatment with significantly lower morbidity.

However, focal therapy is not an alternative to active surveillance in low-risk men but has its greatest role in men with clinically significant, localised, targetable disease who place greater value on maintaining genitourinary function than certainty over long-term disease control.5

Who is suitable for focal therapy?
Men who have unilateral clinically significant prostate cancer that is of intermediate risk are the ideal candidates for focal therapy, with the aim to ensure at least one, if not both, neurovascular bundles remain untreated. To this effect, patients with anterior disease can be treated with needle-based therapies. Patients with disease close to, or just over, the midline can also be treated provided that the contralateral nerve bundle is spared treatment. If sparing at least one neurovascular bundle is not achievable then it is more likely that the functional outcome advantage of focal therapy is compromised (see Figure 2).

Counselling men suitable for focal therapy
In suitable men, treatment options should be described that outline the ‘conventional’ whole gland options as well as the focal therapy approach. The potential strengths and weaknesses of each approach are discussed as they individually apply to each patient.

In a typical case, there is a clear advantage in terms of side-effects with focal therapy, but also uncertainty about long-term cancer control when compared with the more established surgical or radiotherapy options.5 Consideration must also be taken regarding the more intensive follow up that is typically required after focal therapy. Men can be attracted to the

Figure 2. Types of focal therapy using high-intensity focused ultrasound (HIFU) carried out in men with non-metastatic prostate cancer.14 (Re-used under a Creative Commons CC-BY licence)
low side-effects of HIFU, noting that they have options to re-treat with focal therapy or undergo salvage radical treatment in the future, if required.6

What do we expect from radical treatment in this group? The PIVOT study is a robust level 1 study demonstrating contemporary assessment of the impact of radical therapy as compared with observation in prostate cancer.1 Improvements in overall survival are only demonstrated in carefully selected patients, at a cost of functional morbidity and reduction in quality of life. A considerable limitation is the proportion of patients diagnosed with low-risk disease (75%), which currently would likely have been managed with active surveillance.

Evidence acquisition for HIFU in partial ablation setting The UK has produced some of the best evidence for focal therapy with HIFU. Researchers developed the hypothesis in a series of carefully conducted studies, and started a national cohort study (INDEX) and a national registry (HEAT registry).7, 8 An initial feasibility study for a randomised controlled trial (RCT) (PART- ISRCTN17249875) demonstrated the feasibility for randomising suitable men between surgery and HIFU, including the challenges faced in achieving patients and clinician equipoise.9 The PART study plans to evaluate a different ablation technology (photodynamic therapy) which has level 1 evidence pertaining to the treatment of low-risk disease.10

The CHRONOS study (ISRCTN17796995) is an RCT comparing all focal therapies in frequent use (HIFU and cryotherapy), and includes the main radical therapies, surgery and radiotherapy.11 Patients who cannot commit to randomisation due to a lack of equipoise can join the study in CHRONOS-B, which allows the focal ablation to continue with randomisation between focal therapy alone and two neoadjuvant therapies (currently, finasteride or bicalutamide). This more flexible design is aimed to:
1. increase the ability to recruit men into the study;
2. provide comparative data against whole gland therapy;
3. test the hypothesis that cytoreduction (ie, gland or tumour shrinkage) can improve outcomes from ablation while conferring minimal side-effects associated with the neo-adjuvant treatment.

Through the trials and the national registries, clinicians offering HIFU meet the NICE guidance for HIFU treatment (IPG424, NG131) and will address the key concerns of the urological community about minimally invasive treatment for prostate cancer.12

HIFU focal therapy results to date The largest study reviewing the use of focal HIFU (Sonablate) demonstrates oncological control (failure-free survival) of 88% after five years with considerable preservation of genitourinary function. Up to 98% of men reviewed had reported pad-free continence after three years.7, 9 Erectile function was not reported in this study; however, a short-term study evaluated erectile function after one year, with 76.9% of participants maintaining erections. The trifecta of oncological control, pad-free continence and erectile function at 1 year was 53.7%.13

Monitoring and re-treatment after HIFU Consensus groups advocate the follow up of patients to undergo 3–6 monthly PSA tests, and a 12-month mpMRI to determine suspicion of recurrent disease (see Figure 3).2 Targeted biopsies are commonly mandated in research protocols; however, they would normally only be advocated if PSA kinetics or MRI results indicate concern regarding recurrent disease. MRIs would also prove helpful to investigate complications associated with focal therapy, or for training purposes in the early experience of practitioners. Feedback and support from a mentor regarding post-therapy images are also essential.

Patients with localised recurrent disease may be offered a second treatment of focal therapy independent
of whether it is in-field or out-of-field of original treatment. In cases with high volume or extraprostatic disease, transition to whole-gland treatments are typically recommended. Such cases exhibit a worse biology and may reflect an unrecognised adverse pathology from the outset. The results from surgery and radiotherapy are both good, with surgery patients having similar complication and continence rates but a poorer recovery of erections.\textsuperscript{2,6}

**Conclusion**

HIFU is established as an effective form of prostate focal therapy. In men appropriately selected for treatment, the side-effects are lower than for surgery and radiotherapy, and medium-term cancer outcomes appear acceptable and possibly equivalent. RCTs are currently recruiting to provide more solid data, and earlier cohorts of patients will continue to be studied so that long-term outcomes can be better understood.

As increasing numbers of men find this treatment approach a reasonable choice when it is suitable, the availability of HIFU should be increased and multidisciplinary teams should ensure that men are informed when focal therapy may be appropriate, even if it is not locally available. Failure to inform suitable men could lead to a perception of incomplete counselling and consent.

**Declaration of interests**

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