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A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer

Stephanie Guillaumier[a,b,†], *Max Peters*[c,†], *Manit Arya*[b,d,e], *Naveed Afzal*[f], *Susan Charman*[a], *Tim Dudderidge*[g], *Feargus Hosking-Jervis*[a,h], *Richard G. Hindley*[i], *Henry Lewi*[j], *Neil McCartan*[a,b], *Caroline M. Moore*[a,b], *Raj Nigam*[k], *Chris Ogden*[l], *Raj Persad*[m], *Karishma Shah*[a], *Jan van der Meulen*[n], *Jaspal Virdi*[e], *Mathias Winkler*[d], *Mark Emberton*[a,b], *Hashim U. Ahmed*[a,d,h,*]

[a] *Division of Surgery and Interventional Sciences, University College London, London, UK;* [b] *Department of Urology, UCLH NHS Foundation Trust, London, UK;* [c] *Department of Radiotherapy, University Medical Centre, Utrecht, The Netherlands;* [d] *Imperial Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK;* [e] *Department of Urology, The Princess Alexandra Hospital NHS Trust, Harlow, UK;* [f] *Department of Urology, Dorset County Hospital NHS Trust, Dorset, UK;* [g] *Department of Urology, University Hospital Southampton NHS Trust, Southampton, UK;* [h] *Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK;* [i] *Department of Urology, Basingstoke and North Hampshire Hospital, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK;* [j] *Springfield Hospital, Chelmsford, UK;* [k] *Department of Urology, Royal County Surrey Hospital NHS Trust, Guildford, UK;* [l] *Department of Academic Urology, The Royal Marsden Hospital NHS Foundation Trust, London, UK;* [m] *Department of Urology, Southmead Hospital, North Bristol NHS Trust, Bristol, UK;* [n] *London School of Hygiene and Tropical Medicine, London, UK*

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Abstract

Background: Clinically significant nonmetastatic prostate cancer (PCa) is currently treated using whole-gland therapy. This approach is effective but can have urinary, sexual, and rectal side effects.
Objective: To report on 5-yr PCa control following focal high-intensity focused ultrasound (HIFU) therapy to treat individual areas of cancer within the prostate.
Design, setting, and participants: This was a prospective study of 625 consecutive patients with nonmetastatic clinically significant PCa undergoing focal HIFU therapy (Sonablate) in secondary care centres between January 1, 2006 and December 31, 2015. A minimum of 6-mo follow-up was available for599 patients. Intermediate- or high-risk PCa was found in 505 patients (84%).
Intervention: Disease was localised using multiparametric magnetic resonance imaging (mpMRI) combined with targeted and systematic biopsies, or transperineal mapping biopsies. Areas of significant disease were treated. Follow-up included prostate-specific antigen (PSA) measurement, mpMRI, and biopsies.
Outcome measurements and statistical analysis: The primary endpoint, failure-free survival (FFS), was defined as freedom from radical or systemic therapy, metastases, and cancer-specific mortality.
Results and limitations: The median follow-up was 56 mo (interquartile range [IQR] 35–70). The median age was 65 yr (IQR 61–71) and median preoperative PSA was 7.2 ng/ml (IQR 5.2–10.0). FFS was 99% (95% confidence interval [CI] 98–100%) at 1 yr, 92% (95% CI 90–95%) at 3 yr, and 88% (95% 85–91%) at 5 yr. For the whole patient cohort, metastasis-free, cancer-specific, and overall survival at 5 yr was 98% (95% CI 97–99%), 100%, and 99% (95% CI 97–100%), respectively. Among patients who returned validated questionnaires, 241/247

† These authors contributed equally to this work and share first authorship.
* Corresponding author. Imperial Urology, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, London, UK.
E-mail address: hashim.ahmed@imperial.ac.uk (H.U. Ahmed).

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(98%) achieved complete pad-free urinary continence and none required more than 1 pad/d. Limitations include the lack of long-term follow-up.
Conclusions: Focal therapy for select patients with clinically significant nonmetastatic prostate cancer is effective in the medium term and has a low probability of side effects.
Patient summary: In this multicentre study of 625 patients undergoing focal therapy using high-intensity focused ultrasound (HIFU), failure-free survival, metastasis-free survival, cancer-specific survival, and overall survival were 88%, 98%, 100%, and 99%, respectively. Urinary incontinence (any pad use) was 2%. Focal HIFU therapy for patients with clinically significant prostate cancer that has not spread has a low probability of side effects and is effective at 5 yr.

1. Introduction

The therapeutic approach to nonmetastatic prostate cancer is an outlier compared to strategies for other solid organ cancers. Regardless of the burden or location of cancer within the gland, treatment is directed at the whole gland using surgery or radiotherapy. While both approaches are effective, they can be associated with urinary incontinence and erectile dysfunction, with radiotherapy occasionally causing rectal side effects [1–3]. While current trends demonstrate that radical therapy is increasingly used among the patients most likely to benefit from treatment with respect to better cancer-specific survival [4], there is still a need to reduce treatment-related side effects, particularly as the survival benefit conferred by radical treatment is often seen over 10–15 yr when compared to a strategy of active monitoring [5].

The aim of focal therapy is to reduce side effects and maintain cancer control by targeting areas of known cancer in a similar approach to that for other solid organ cancers [6–8]. This concept of tissue preservation has come about through improvements in disease localisation using multiparametric magnetic resonance imaging (mpMRI) and mapping biopsy techniques [9]. However, many studies have hitherto been small, based in expert centres, or subject to short follow-up [10–18]. The only randomised study to evaluate focal therapy recruited patients with low-risk disease [19], a population known to have little to no chance of metastases or cancer-related mortality.

We now report on medium-term cancer control outcomes in a large multicentre patient cohort with clinically significant nonmetastatic prostate cancer treated with focal therapy using high-intensity focused ultrasound (HIFU).

2. Patients and methods

Institutional review board exemption was granted by University College London Hospital for our health technology assessment programme, which followed guidelines for evaluating surgical interventions [20,21]. Focal HIFU commenced in 2006 in the UK with approval for clinical use by the National Institute for Health and Care Excellence (NICE) under special arrangements. All cases had to be prospectively and consecutively entered into an academic registry, discussed in a multidisciplinary meeting, and given written information on the advantages and disadvantages of the procedure. We previously reported on medium-term outcomes following whole-gland HIFU [22]. Between January 1, 2006 and December 31, 2015, 625 consecutive patients underwent primary focal HIFU using a Sonablate 500 device (Sonacare Inc., Charlotte, NC, USA) in nine centres. Focal HIFU treatment was offered to patients diagnosed with nonmetastatic prostate cancer of Gleason score 6–9 and stage T1c–3bN0M0 and prostate-specific antigen (PSA) of $\leq$30 ng/ml. Gleason 6 disease required a minimum of 4 mm of cancer [23]. Patients were classified into D'Amico low-, intermediate-, and high-risk groups [24].

Disease was localised using mpMRI combined with targeted and systematic biopsies, or transperineal mapping biopsies. Targeted biopsies involved taking three to six biopsy cores from all lesions with a Likert score of 3–5, as well as systematic biopsies (transperineal or transrectal). Mapping biopsies involved taking biopsy cores every 5 mm. Intermediate- and high-risk cases also underwent a radioisotope bone scan and/or cross-sectional computed tomography to rule out distant metastases, depending on local institution guidelines.

All surgeons underwent a rigorous period of training involving online learning, observation of five cases on two separate occasions in an expert centre, and on-site proctoring by an expert urologist for five to ten cases, and were followed by an expert clinical applications specialist for all subsequent treatments.

There were various forms of focal HIFU permitted (Fig. 1). Up to two retreatments with focal HIFU were allowed. All men were advised to undergo 3–6-monthly PSA testing, with mpMRI routinely performed at 1 yr and every 1–2 yr. Two rises in PSA after the nadir, without predefining the magnitude of the rise, were investigated using prostate biopsy or mpMRI followed by biopsy if the mpMRI was suspicious. We have previously reported on the high negative predictive value of mpMRI following focal-HIFU [23,25].

Repeat HIFU was offered when either (1) clinically significant cancer on biopsy occurred in field or out of field and mpMRI staging indicated that the disease was still localised, or (2) when mpMRI demonstrated clear in-field recurrence (mpMRI Likert score 5) associated with a rising PSA. Patients were routinely offered the option of radical prostatectomy or radical radiotherapy.

Physicians assessed postoperative adverse events during follow-up clinic visits. Functional outcomes were assessed via patient-reported outcome measures using validated questionnaires collected at 1–2 and 2–3 yr after focal HIFU treatment. Validated questionnaires included the International Prostate Symptom Score [26] and the Expanded Prostate Cancer Index Composite (EPIC) urinary continence domain [27]. All data were audited and quality controlled by two data managers (N.M. and F.H.J.).

2.1. Primary outcome

Failure-free survival (FFS) was defined as avoidance of local salvage therapy (surgery or radiotherapy), systemic therapy, metastases, and prostate cancer–specific death. This excluded PSA kinetics, as there are no kinetic measures that are valid in this setting.