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**Title**:

# An exploratory study of dose escalation versus standard focal High Intensity Focused Ultrasound for treating non-metastatic prostate cancer

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## Abstract

### Objective

Analysis of treatment success regarding oncological recurrence rate between standard and dose escalation focal high-intensity focused ultrasound (HIFU) of prostate cancer.

### Materials and methods

In this analysis of our prospectively maintained HIFU (Sonablate® 500) database, 598 patients were identified who underwent a focal HIFU (Sonablate® 500) between March 2007 and November 2016. Follow-up occurred with 3-monthly clinic visits and PSA testing in the first year. Thereafter, PSA was measured 6-monthly or annually at least. Routine and for-cause mpMRI with biopsy for MRI-suspicion of recurrence. Treatments were delivered in a quadrant or hemiablation fashion depending on the gland volume as well as tumour volume and location. Prior to mid-2015, standard focal-HIFU was used (two HIFU blocks); after this date some urologists conducted dose escalation focal-HIFU (3 overlapping HIFU blocks). Propensity matching was used to ensure two matched groups leading to 162 cases for this analysis. Treatment failure was defined by any secondary treatment (systemic therapy, cryotherapy, radiotherapy, prostatectomy, or further HIFU), metastasis from prostate cancer without further treatment, tumour recurrence with Gleason score >/=7 (>/=3+4) on prostate biopsy without further treatment, or prostate cancer-related mortality. Complications and side-effects were also compared.

### Results

Median age was 64.5 years (IQR 60-73.5) in the standard focal-HIFU group and 64.5 years (IQR 60-69) in the dose-escalation group. Median prostate volume was 37ml (IQR 17-103) in standard group and 47.5ml (IQR 19-121) in the dose-escalation group. As tumour volume on mpMRI and Gleason score were major matching criteria these were identical with 0.43ml (IQR 0.05-2.5) and Gleason 3+3=6 in 1/32 (3%), 3+4=7 in 27/32 (84%), and 4+3=7 in 4/32 (13%). Recurrence in treated areas were found in 10/32 (31%) when standard treatment zones were applied, and in 6/32 (19%) of dose-escalation focal-HIFU (p=0.007).

## Conclusion

This exploratory study shows that dose escalation focal-HIFU may achieve higher rates of disease control compared to standard focal-HIFU. Further prospective comparative studies are needed.



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## Introduction

Focal high intensity focused ultrasound (HIFU) has been increasingly used to treat localised prostate cancer [1] in order to reduce treatment margins from extending to the whole prostate towards areas of tumour [2]. The aim is to target areas of clinically significant prostate cancer accurately whilst conferring a reduction in treatment-related harms [3], provided patients are diagnosed, staged and selected appropriately [4].

Recent results from our own group and others have shown good cancer control in the medium term, with rates of radical or systemic therapy of 10% at 5 years although further sessions of focal HIFU are needed in about 20-30% within the same time period [5,6,7]. Just as with traditional radical therapy, failure can sometimes occur, and like other surgical innovations and technologies, adjustments are often made to technique in order to optimise therapy delivery.

A number of biological reasons might account for why the first focal HIFU is unable to treat all the cancer cells in the area targeted. First, the margin may miss the extent of the tumour. Second, heat-sink effects from vasculature can counteract the thermoablative effect. Third, skip lesions can occur during the treatment. Fourth, energy delivery can be sub-optimal. We tested the hypothesis that dose escalation of HIFU delivery by the application of an additional block of HIFU therapy might overcome these biological issues and improve disease control rates.

## Methods

Institutional review board exemption was granted. Our programme of health technology assessment followed the Medical Research Council (UK) guidelines for evaluating complex interventions [8]; these guidelines were recently incorporated and applied to surgical innovation within the IDEAL framework [9]. Focal transrectal HIFU was a surgical innovation that commenced in 2006 in the UK and approved for clinical use by the UK's National Institute for Health and Clinical Excellence (NICE) under special arrangements. That is, 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 have previously reported on medium

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term outcomes following whole-gland and focal HIFU from this registry [10]. Between 1st/January/2006 and 31st/December/2015, 625 consecutive patients underwent primary focal HIFU for non-metastatic prostate cancer (Sonablate® 500, Sonacare Inc., USA) within 9 centres. Focal HIFU treatment was offered to patients diagnosed with non-metastatic prostate cancer with Gleason 6 through 9, stage T1c-T3bN0M0 and PSA of </=20ng/ml. Gleason 6 required a minimum of 3mm of disease. Disease was localised using mpMRI, combined with targeted and systematic biopsies, or transperineal mapping biopsies. Intermediate and high-risk cases also underwent a radioisotope bone-scan and/or cross-sectional CT to rule-out distant metastases dependent on local guidelines at each hospital.

Treatments were delivered in a quadrant or hemiablation fashion, or for very small lesions a focal with approximate 3mm margin (so-called ultrafocal), depending on the gland volume as well as tumour volume and location. Index lesion ablation alone was conducted in patients with multifocal disease provided untreated areas harboured no more than 3mm of Gleason 6 on systematic or template mapping biopsies. All men were advised to undergo 3 to 6 monthly serum PSA testing. An mpMRI was routinely performed regardless of PSA kinetics at 1 year and approximately 1-2 yearly thereafter. Two rises in PSA after the nadir level was achieved, without predefining the level of rise, was investigated with a prostate biopsy, or mpMRI followed by biopsy if the mpMRI was suspicious. We have previously reported on the high negative predictive value of mpMRI in the post-focal HIFU setting for clinically significant prostate cancer [11]. Clinically significant cancer on biopsy of untreated areas was defined as ‘out-of-field’ progression.

Further focal HIFU was offered when either, a) clinically significant cancer on biopsy occurred in-field or out-of-field and where the mpMRI staging indicated that the disease was still localised or, b) when the mpMRI demonstrated a clear recurrence (mpMRI Likert score 5) in-field associated with a rising PSA. Other considerations for further focal HIFU were the absence of intra-prostatic calcification or difficult disease location such as apical disease overlapping the external urinary sphincter. Patients were also routinely offered the option of radical prostatectomy or radical radiotherapy. All data was audited and quality controlled by two data managers (NM and FHJ).

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Primary outcome for the validation of this dose escalation strategy was based on a composite endpoint of failure-free survival (FFS) with failure defined as residual untreated Gleason 3+4=7 or more cancer on post-treatment biopsy, local salvage therapy (surgery or radiotherapy), systemic therapy, prostate cancer metastases or prostate cancer-specific mortality.

*HIFU protocol*

Treatment planning took place using a 4cm focal length probe for anterior areas of treatment and a 3cm probe for posterior areas. When ablating tissue with HIFU, energy is delivered in repeated three-dimensional focal points over an individual predefined area. Each of such an ablative block covers the tumour with a surrounding safety margin. Prior to mid 2015, two partially overlapping ablative blocks were applied one after the other to target a quadrant or for ultrafocal HIFU in which the tumour resided [Figure 1a]. Following this date, some urologists conducted treatment in 3 layered blocks in order to deliver more energy [Figure 1b]. Those ablative blocks had a bigger overlapping area covering the tumour compared to two blocks. The total delivered energy in Joules was not recorded routinely but the energy per block was delivered in a similar fashion according to visually-estimated focal-HIFU delivery. In other words, energy changes were made to each pulse if necessary to derive greyscale hyper-echoic changes in the focal zone. These hyperechoic ‘pop-corning’ effects are believed to represent steam formation.

*Statistical analysis*

Variables with skewed distribution are presented as medians with interquartile ranges (IQR) and categorical variables as absolute numbers with percentages. Cases were paired with “MatchIt” package. For the purposes of this analysis, information was available on 162 cases in whom standard focal-HIFU or dose-escalation focal-HIFU was carried out. Cases were matched for Gleason score according to biopsies prior to treatment and tumour volume in mpMRI in which matching had to be exact. Other matching criteria, where the nearest concordance within the groups was acceptable, were maximum cancer core length in diagnostic biopsies, length of last follow-up, as well as time to failure. From these, there were a resultant 32 matched pairs (64 cases) which were afterwards re-

analysed individually. Explorative analysis of basic characteristics were performed with Mood's median test, significance level for treatment results in matched pairs was calculated with McNemar's test for paired samples with p-value set at 0.05 for statistical significance. Analyses were performed using the R language environment for statistical computing.

## Results

*Baseline HIFU demographics*

In total, 64 patients were identified and matched. Median age was 64.5 years (IQR 60-73.5) in the standard focal-HIFU group and 64.5 years (IQR 60-69) in the dose-escalation focal-HIFU group. Median prostate volume was 37 ml (IQR 17-103) in standard group and 47.5 ml (IQR 19-121) in the dose-escalation group. Median tumour volume derived from mpMRI was a major matching criterion and therefore in both groups identical with median of 0.425 ml (IQR 0.05-2.5) as was Gleason score (% of cases). [Table 1].

*Treatment outcomes*

There were no differences in rates of urinary tract infections or cystoscopic interventions for necrotic tissue, strictures and bladder neck contractures (Table 2). There were no rectourethral fistula in these matched groups (although our previous reports have shown this risk to be 1 in 500). Recurrences in treated areas were found in 10/32 (31%) when standard focal-HIFU treatment zones were applied, and in 6/32 (19%) when dose-escalation focal-HIFU was used (p=0.007). The time that had elapsed until treatment failure was proven and the length of follow-up without any proof of recurrence were 12.5 months (IQR 12-22.75) and 23 months (IQR 13-26.75) in standard focal-HIFU group, respectively. For the dose-escalation focal-HIFU group, these were 11.5 months (IQR 9.5-12.75) and 13.5 months (IQR 12-26.5), respectively [Table 2].

## Discussion

In summary, we have shown that dose escalating in the delivery of focal-HIFU leads to improved cancer control compared to standard focal-HIFU delivery without significant impact on adverse events post-operatively. Our study reports on a technical innovation

that aims to improve cancer control whilst minimising the impact on function and adverse events.

Whenever there are new treatment modalities, adjustments were made. Radical prostatectomy is one such example. Hugh Hampton Young developed radical prostatectomy back in 1904, with Millins describing in 1947 the retropubic approach and in 1983 Patrick Walsh the anatomic radical prostatectomy, with subsequent advances in laparoscopic and robotic assisted approaches. There were also several amendments made in other urological cancer treatments such as focal radiofrequency ablation in kidney tumours, until it was a standard care therapy [13].

In the minimally-invasive treatment of prostate cancer there was a key change from whole to partial ablations which now often is applied to treatment of the index lesion [3]. Manufacturer modifications have been made to the devices with improvements in hardware and software. Uchida et al. recently demonstrated what the impact of these changes were in a large consecutive series with upgraded HIFU devices following whole-gland HIFU [14] whilst there has also been a recent change in another device from Ablatherm to Focal-One with a number of additional features [12].

Our series points to a reduced recurrence rate after escalated energy doses with a third treatment block; this might be explained by several factors. First, more energy is absorbed by the prostate tissue leading to an improved coagulative necrosis. It is known from the underlying basic principles in HIFU therapy that the area in which a sufficient high temperature for tissue ablation is reached is restricted to a focal point. Around this limited area there is a rapid drop in temperature and therefore insufficient energy applied for tissue destruction [15]. Second, there is a possibility that during treatment areas of untreated tissue that are in-between delivered pulses shift in space due to swelling causing skip-lesions that are then not treated during subsequent pulses. Shoji et al demonstrated a partial shift of the prostate on the basis of local tissue swelling during HIFU of approximately 13% volume increase and linear shifts of up to 5.5mm [16].

When reducing HIFU from whole gland to hemiablation still 3 ablative blocks were given even when the lesion being treated was in the peripheral zone and small [17]. Under



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further reducing of the ablative areas to quadrant ablations posterior tumours were initially only treated with 2 blocks. Although an adequate margin was treated more recurrences were found compared to those earlier treated with an additional block. By hitting a quadrant threefold it was hypothesized to ensure high energy levels to overcome a heatsink effect and also the effect of skip lesions [16].

There are limitations to this study. Although it is a matched pair analysis it nonetheless is a retrospective analysis with a modest sample size and there might be unknown residual confounders that impact on treatment delivery. Whilst a prospective randomised trial to assess the different techniques might be possible this may not justify the significant resource issues involved in delivering such a trial. Our follow-up period is short. This is a consequence of the recent adoption of this type of dose-escalation for focal HIFU and therefore the follow-up for this group and the matched paired was inevitably shorter than what we have previously reported for the entire focal-HIFU cohort.

**Conclusion**

This exploratory study shows that dose escalation focal-HIFU may achieve higher rates of disease control compared to standard focal-HIFU. Long term outcomes, ideally from comparative effectiveness studies, for focal HIFU in treating non-metastatic prostate cancer are awaited.

**Authorship**

PH, HUA, SG and NM were responsible for data collection, analysis of the data. HUA and PH were responsible for production of the first draft. PH and HUA completed the data analysis. All authors were involved in data collection, manuscript preparation/drafting and approval of the final draft. HUA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HUA is guarantor of the study.

**Declaration of Interests**

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Emberton receives research support from the United Kingdoms's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Institute. He is an NIHR Senior Investigator. Emberton receives funding from NIHR-i4i, MRC, Cancer Research UK, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical.

Moore receives funding from the National Institute for Health Research, The European Association of Urology Research Foundation, Prostate Cancer UK, Movember and the Cancer Vaccine Institute, for clinical prostate cancer research. She has received advisory board fees for Genomic Health.

Ahmed, Emberton, Hindley, Moore, Boxler and Arya are all proctors for HIFU and are paid for training other surgeons in this procedure.

Emberton, Freeman and Hindley have loan notes/stock options in Nuada Medical Ltd (UK).

Winkler receives a travel grant and a loan of device from Zicom Biobot.

None of the other authors have anything to declare.

**Role of Funding Source**

None of the funding sources had any role or input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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Abbreviations

PSA – prostate specific antigen

mpMRI – multiparametric MRI

HIFU – high intensity focused ultrasound

FFS – Failure-free survival

IQR – inter-quartile range

SD – standard deviation



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**Table 1. Baseline demographics**



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| Variable | Standard Focal-HIFU protocol | | Dose-escalation Focal-HIFU protocol | | p-value |
|---|---|---|---|---|---|
| | Median/N | IQR/% | Median/N | IQR/% | |
| Age at treatment (in years), median, (IQR) | 64.5 | 60 – 73.5 | 64.5 | 60 – 69 | 1.000 |
| ADT pre-treatment, N, (%) | 4 | 13% | 0 | 0% | 0.113 |
| PSA pre-treatment, median, (IQR) | 7.0 | 4.72 – 10.55 | 6.9 | 5.33 – 8.21 | 1.000 |
| Prostate volume (MRI, in ml), median, (range) | 37 | 17 – 103 | 47.5 | 19 – 121 | 0.058 |
| Tumour volume (MRI, in ml), median, (range) | 0.43 | 0.05 – 2.5 | 0.43 | 0.05 – 2.5 | 1.000 |
| | | | | | |
| Biopsy results pre-treatment, median, (IQR) | | | | | |
| *no. positive cores* | 4.5 | 3 – 7.25 | 4 | 3 – 5.25 | 0.127 |
| *total cores* | 15 | 9 – 34.5 | 10 | 6 – 17 | 0.012 |
| *MCCL (in cm)* | 6 | 3.75 – 9 | 5 | 4 – 8 | 0.121 |
| *max. percentage of core (%)* | 50 | 30 – 80 | 55 | 32.5 – 65.5 | 0.789 |
| | | | | | |
| Gleason score pre-treatment, median | 3+4 | | 3+4 | | |
| *3+3, N, (%)* | 1 | 3% | 1 | 3% | 1.000 |
| *3+4* | 27 | 84% | 27 | 84% | 1.000 |

| | | | | | |
|---|---|---|---|---|---|
| *4+3* | 4 | 13% | 4 | 13% | 1.000 |
| | | | | | |
| T-stadium pre-treatment, median | T2 | | T2 | | |
| *T1c, N, (%)* | 2 | 6% | 1 | 3% | 1.000 |
| *T2* | 24 | 75% | 28 | 88% | 0.337 |
| *T3a* | 6 | 19% | 3 | 9% | 0.474 |

Abbreviations: N, number; IQR, inter quartile range; ADT, androgen deprivation therapy; MRI, magnetic resonance imaging; ml, millilitres; MCCL, maximum cancer core length; cm, centimetre; CDC, Clavien Dindo Classification; UTI, urinary tract infection; LA, local anesthesia; GA, general anesthesia.



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**Table 2. Adverse events and cancer control outcomes**

| Determinant | Standard Focal-HIFU protocol | | Dose-escalation Focal-HIFU protocol | | p-value |
|---|---|---|---|---|---|
| | Median/N | IQR/% | Median/N | IQR/% | |
| Recurrence in treated area, N, (%) | 10 | 31% | 6 | 19% | 0.007 |
| Time to recurrence (months), median, (IQR) | 12.5 | 12 – 22.75 | 11.5 | 9.5 – 12.75 | 0.515 |
| Follow-up without recurrence (months), median, (IQR) | 23 | 13 – 26.75 | 13.5 | 12 – 26.5 | 0.090 |
| Complications post HIFU (CDC), N, (%) | | | | | |
| *Grade II: UTI (in first 6 month)* | 2 | 6% | 0 | 0% | 0.492 |
| *Grade IIIa: cystoscopy (in LA)* | 1 | 3% | 2 | 6% | 1.000 |
| *Grade IIIb: bladder neck incisions/resections (in GA)* | 0 | 0% | 2 | 6% | 0.492 |
| Abbreviations: N, number; IQR, inter quartile range | | | | | |



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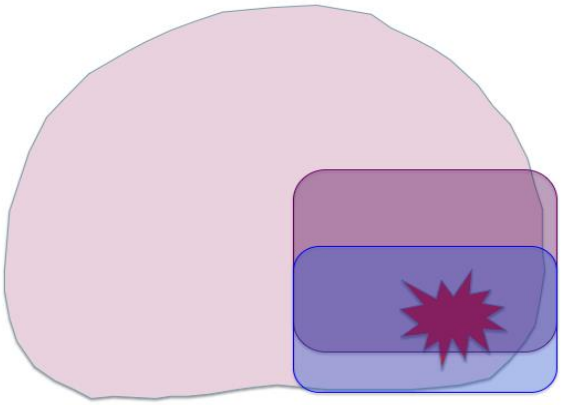

Figure 1a. Standard 2 block approach to focal HIFU (Sonablate, Sonacare Inc) for the treatment of non-metastatic prostate cancer

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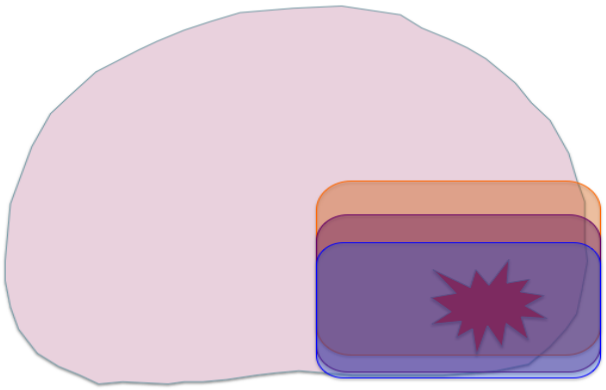

Figure 1b. Dose escalation using 3 blocks of treatment layered approach to focal HIFU (Sonablate, Sonacare Inc) for the treatment of non-metastatic prostate cancer