

**PSA versus MR imaging parameters for assessing oncological outcomes following  
HIFU focal therapy for localised prostate cancer**

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## **Abstract**

### ***Introduction***

Focal therapy for localised prostate cancer has the potential for oncological control without the side effects of radical therapies. However, there is currently no validated method for monitoring treatment success. We assessed the diagnostic performance of PSA parameters and MRI compared to histological outcomes following focal therapy.

### ***Patients and Methods***

Patients from three Ethics Review Board approved prospective studies of focal HIFU (Sonablate 500™) for localised prostate cancer (T1c-T3a, Gleason grade  $\leq 4+3$ , PSA  $\leq 20$ ). Post-HIFU prostate specific antigen (PSA) nadir, 6-month PSA, PSA density, and early ( $<3$  week) and late (6-month) MRI (T2 weighted, dynamic contrast enhanced +/- diffusion-weighted) was assessed for predictive accuracy of cancer on post-operative biopsy, using Receiver Operating Characteristic (ROC) analysis and sensitivity, specificity and positive (PPV) and negative (NPV) predictive estimates. ROC areas for MRI and PSA were compared. Calculations for statistical significance ( $p$ -value  $\leq 0.05$ ) were obtained in a subset of patients comparing area under ROC for 6-month MRI and PSA criteria, across 4 different histological definitions of disease significance.

### ***Results***

111/118 men underwent at least one post-operative biopsy (median 6 cores), with an overall positive biopsy rate of 37% (41/118), over a mean follow-up period of 716

days post-HIFU. Area under ROC for early and late MRI were (depending on definition of significant disease) 0.65–0.76, and 0.77–0.85, respectively, with sensitivity, specificity and negative predictive values of 68-91%, 52-55% and 85-98% (early MRI) and 63-80%, 67-73% and 86-97% (late MRI). The area under the ROC curve was statistically significantly higher for late MRI than 6 month and nadir PSA for residual disease >3mm or any Gleason 4 tumour.

### ***Conclusions***

Early and later MRI performed better than PSA measurements in the detection of residual tumour after focal therapy.

## **1. Introduction**

Focal therapy is an emerging treatment for localised prostate cancer, using a range of technologies (1-6). Early reports of HIFU and cryotherapy have demonstrated low rates of genitourinary side-effects, in conjunction with acceptable short-term cancer control (7). However, one of the principal concerns in focal therapy is the lack of a validated, non-invasive test for monitoring oncological outcome (8). Whilst PSA parameters are an established means of monitoring biochemical outcomes after radical treatment, their value after focal treatment is less certain, because of the variable contribution of residual prostate.

Biopsy is invasive, with an associated risk of significant morbidity (9) and we know that systematic biopsies for small foci of tumour are subject to considerable under-sampling and under-grading compared to targeted samples (10). Conversely, imaging has the capability of visually monitoring the whole prostate (treated and untreated areas) and of providing information on changes in characteristics that might signal residual disease, progression of untreated secondary lesions, or development of de novo lesions. MRI has also shown good performance for the detection of residual tumour after whole prostate HIFU ablation, with sensitivities for detection residual disease of 73-87% (11).

We aimed to assess the diagnostic performance of PSA parameters and mpMRI for the detection of residual disease found at biopsy after focal HIFU, using four histological threshold definitions of significant disease.

## **2. Patients and Methods**

### *2.1 Patients*

Three early development studies evaluating focal HIFU treatment (Sonablate 500®) for localised prostate cancer have now been completed at our institutions. Research committee approval and written, individual patient consent was obtained for each study. In the first study (n=20) (1), treatment was delivered as a hemi-ablation to unilateral disease; in the second study (n=42) (2), treatment involved more targeted 'focal' ablation of cancer lesion(s), and in the third (n=56), 'index lesion' ablation was performed to the dominant clinically significant lesion(s) only (3). The HIFU treatments occurred between 2006 and February 2011, and all men entered a prospective HIFU registry on completion of the study period, for collection of on-going oncological (including PSA, mpMRI, biopsy) and quality of life data. All of the 118 patients in these trials were included.

Short-term (12-month) adverse event, genitourinary functional, biochemical and histological outcomes have been published on the results on all three studies (1-3). The purpose of this current report was to assess the accuracy of MRI and PSA outcomes against histopathology on all participants within the three studies who underwent at least one post-HIFU biopsy. Additionally, this analysis includes registry data extending beyond the 12-month outcomes previously published (1-3).

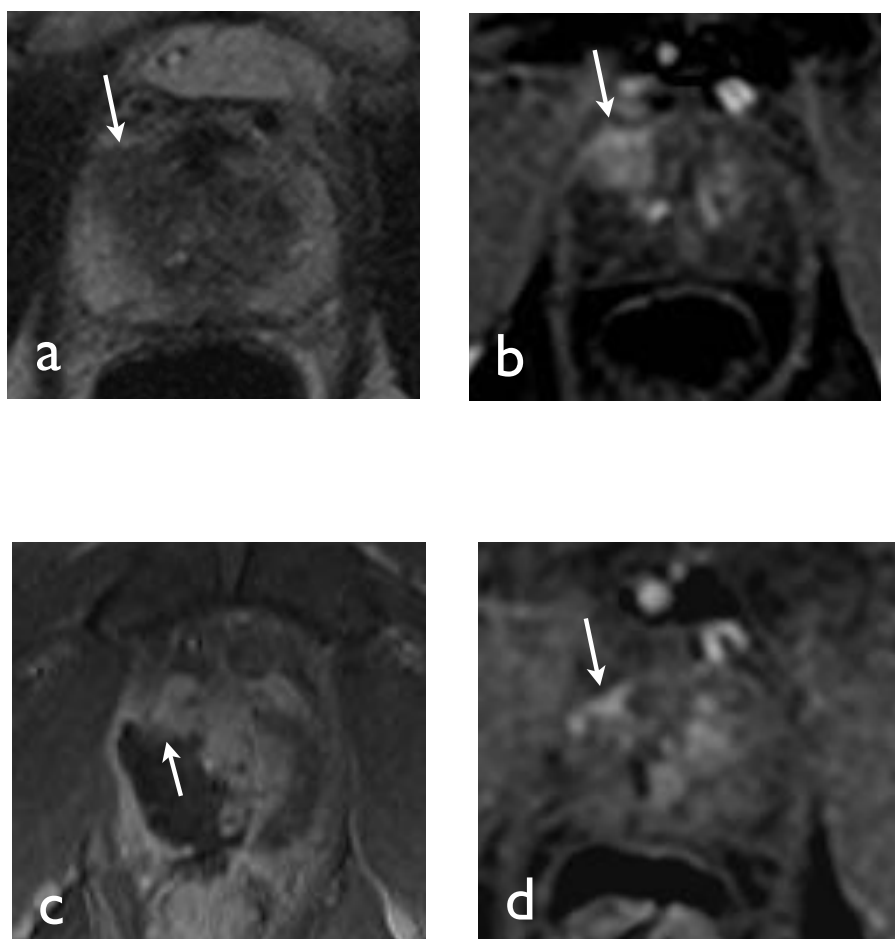
### *2.2 MRI*

All pre- and post-HIFU MRI was performed using either a 1.5 Tesla or 3 Tesla MRI scanner and a pelvic phased array receiver, pelvic coil, full protocol of T1 and T2

weighted turbo-spin echo images and dynamic post gadolinium volume acquisition. Diffusion-weighted images were also obtained in all patients pre-HIFU and in 15 patients post-HIFU (6-month scan) (appendix table A).

The early MRI was performed between 48 hours and 3 weeks post-HIFU, as a preliminary assessment of treatment quality, with coverage of the tumour scored between 1 and 3 (1 indicating the lowest suspicion of residual tumour). If the margin of the non-enhancing prostate was close to the treated tumour we scored 2, and 3 if there was enhancement in the tumour location.

The late MRI was performed at approximately 6-months, pre- follow-up biopsy. This was the earliest stage that evidence of any residual tumour was expected to become apparent. Prior to this time, resolving necrotic tissue has been found to mask residual cancer (12). Early and late MRI were reported and graded prospectively by one of a group of specialist urologists with at least 3 years of prostate MRI experience. A 5-point Likert-type scale for likelihood of residual tumour was used, with a score of 3 or higher considered positive (as per standard departmental practice, prior to the introduction of the PI-RADS scoring system™). In a few cases where no score had been assigned prospectively, the images were reviewed and graded retrospectively by a single experienced urologist (AK), without knowledge of the post-treatment histological outcome.



**Figure 1.** MRI images before (*a* and *b*), early post (*c*), and 6 months post focal HIFU to a Gleason 3+4 right anterior lesion. The lesion is shown on T2 (*a*) and dynamically enhanced (*b*) images (arrow in each) before treatment. Early post HIFU (*c*) the treatment margin is close to the location of the tumour (arrow) and the score was equivocal for residual tumour (score 2). Late post HIFU (*d*) a rim of enhancement at the site of the tumour was scored as positive on MRI (score 5) and the biopsy was positive for all definitions of significance.

### *2.3 PSA*

Serum PSA levels were obtained pre-HIFU, and at 6 weeks, 3, 6, 9, 12 months, and approximately 6-monthly thereafter. PSA nadir was calculated as the lowest PSA achieved at any point following focal-HIFU. Post-operative PSA density was calculated as 6-month PSA level divided by the volume of residual tissue, as assessed by the 6-month post-HIFU MRI.

### *2.4 Biopsies*

A limited number of representative biopsies were taken at 6-months from the treated area of the prostate, at an approximate density of 1 per millilitre of residual tissue as assessed on ultrasound. If the late MRI indicated any areas of suspicion, these were also targeted at biopsy (cognitive targeting). This protocol was standardised across all of the focal therapy studies included in this analysis. Additional, 'for-cause' biopsies were performed in some men with on-going suspicion of residual tumour in later follow-up (either a suspicious MRI or continuing rise in PSA). Only biopsies in the area of the treatment were included in our analysis.

### *2.5 Disease stratification*

In order to differentiate between different burdens of residual tumour, and to assess thresholds for detection by imaging and biochemical parameters, we divided post-HIFU tumour into the following categories:

1. Any cancer



2. Gleason pattern 4 or 5 *and/or* >3mm maximum cancer core length (UCL definition 2) (13).
3. >3mm maximum cancer core length (any disease grade)
4. Gleason pattern 4 or 5 (any cancer core length)

### *2.6 Statistical analysis*

PSA nadir, 6-month post-operative PSA, post-operative PSA density, early and late MRI outcomes were assessed for predictive accuracy of histological residual tumour on post-operative biopsy using area under the Receiver Operating Characteristic (AUROC) analysis. All figures given are for fitted curves produced with the online ROC calculator ROCfit, which generates the maximum likelihood fit of a binormal model (14). We performed two analyses: firstly using only the 6-month biopsy data, and secondly including the result of any positive biopsy. Areas under the ROC curve for MRI and the PSA criteria were compared using the method described by Hanley (15).

Additionally, estimates of sensitivity, specificity and positive (PPV) and negative (NPV) predictive values were calculated after dichotomising the MRI results so that equivocal scans were considered positive (2 or 3 considered positive on the early scan, and 3-5 considered positive at 6 months)

## **3. Results**

Of 118 men with localised prostate cancer (T1c-T3a, Gleason grade  $\leq 4+3$ , PSA  $\leq 20$ ) who underwent focal ablation within any of the three prospective 12-month studies,

111 received at least one post-operative biopsy (at a median of 190 days post-HIFU, with a median of 6 cores). Sixteen of these men received a second ‘for cause’ biopsy (a mean 716 days post-HIFU), due to suspected residual or recurrent tumour (usually a suspicious MRI or a rise in PSA). Baseline characteristics are detailed in appendix table B.

109 of the 111 men with a 6-month biopsy also had a 6-month MRI and full PSA data. This group was used to analyse both the performance of 6-month MRI and PSA measurements. The performance of early MRI was assessed using a smaller group of 105 men who underwent a scan at <1 month and biopsy at 6 months.

### 3.1 Biopsy Outcomes

Twenty-eight men (25%) had residual disease on first biopsy, of whom 12/28 (43%) fulfilled our criteria 2, 3, or 4 for clinically significant disease. After for-cause biopsy, a total of 41 men (37%) had received a positive biopsy post-treatment, of whom 21/41 (51%) fulfilled criteria 2, 3 or 4 for clinical disease significance. The median cancer core length of residual disease on any biopsy was 2mm (range 1–10mm).

	Any disease	>3mm CCL or any Gleason 4	>3mm CCL	Any Gleason pattern 4
<b>After initial biopsy</b>	28 (25%)	12 (11%)	10 (9%)	7 (6%)
<b>After any biopsy</b>	41 (37%)	21 (19%)	14 (13%)	14 (13%)

**Table 1.** Disease detection on initial and subsequent biopsy according to different levels of disease burden

### 3.2 PSA Parameters

The median pre HIFU PSA was 7ng/ml, and median post treatment nadir, 6-month, and PSA density values were 1.6, 2.0 and 4.5ng/ml respectively. Six-month and nadir PSA levels demonstrated similar AUROC accuracies for residual disease detection against initial biopsy (0.63 - 0.71). For both groups, additional information on subsequent biopsy resulted in globally reduced accuracy rates. The results for PSA density were similar, but with a higher accuracy (0.78) for the detection of Gleason 4 or 5 disease.

<b>INITIAL BIOPSY (standard errors in brackets)</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>PSA nadir</b>	0.63 (0.055)	0.64 (0.072)	0.71 (0.066)	0.66 (0.096)
<b>6 month PSA</b>	0.64 (0.052)	0.65 (0.068)	0.71 (0.058)	0.67 (0.092)
<b>PSA density</b>	0.64 (0.070)	0.66 (0.070)	0.67 (0.077)	0.78 (0.064)
<b>ANY BIOPSY (standard errors in brackets)</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>PSA Nadir</b>	0.58 (0.053)	0.56 (0.064)	0.67 (0.070)	0.54 (0.077)
<b>6 month PSA</b>	0.58 (0.053)	0.56 (0.065)	0.67 (0.066)	0.50 (0.081)
<b>PSA density</b>	0.62 (0.054)	0.59 (0.073)	0.67 (0.082)	0.59 (0.093)

**Table 2.** ROC characteristics of PSA parameters against initial and subsequent biopsy.

The p values for the comparison of the PSA parameters AUC with that for 6 month MRI (Table 4) are given in appendix table C.

### 3.3 MRI

#### 3.3.1 *Early MRI*

105 men received an early MRI (at a median of 15 days after biopsy, range 7-29) of which 54 (51%) were considered equivocal or positive. Moderate accuracy rates were achieved for predicting the presence of residual cancer, with AUROC ranging between 0.65 and 0.76. Negative predictive value for residual tumour was high (85% for any tumour, but 98% for the three definitions of significant disease), but positive predictive values were low across all disease categories (ranging 9.4%–32.1%).

<b>INITIAL BIOPSY</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>Sensitivity (%)</b>	17/25 (68%)	10/11 (91%)	9/10 (90%)	5/6 (83%)
<b>Specificity (%)</b>	44/80 (55%)	51/94 (54%)	51/95 (54%)	51/99 (52%)
<b>PPV (%)</b>	17/53 (32%)	10/53 (19%)	9/53 (17%)	5/53 (10%)
<b>NPV (%)</b>	44/52 (85%)	51/52 (98%)	51/52 (98%)	51/52 (98%)
<b>ROC (standard error)</b>	0.65 (0.070)	0.76 (0.063)	0.76 (0.067)	0.75 (0.11)
<b>ANY BIOPSY</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>Sensitivity (%)</b>	25/37 (68%)	15/19 (79%)	12/14 (86%)	8/12 (67%)
<b>Specificity (%)</b>	40/68 (59%)	48/86 (56%)	50/91 (55%)	48/93 (52%)
<b>PPV (%)</b>	25/53 (47%)	15/53 (28%)	12/53 (23%)	8/53 (15%)
<b>NPV (%)</b>	40/52 (77%)	48/52 (92%)	50/52 (96%)	48/52 (92%)
<b>ROC (standard error)</b>	0.69 (0.064)	0.72 (0.063)	0.75 (0.064)	0.64 (0.10)

**Table 3.** Accuracy rates of early MRI against initial and subsequent biopsy

When early MRI outputs were correlated with the outcomes of any positive biopsy, including repeat biopsy in those 16 men receiving one, sensitivity and negative predictive values decreased marginally for the detection of clinically significant tumour. However, specificity rates remained similar, and positive predictive values improved.

### *3.3.2 Later MRI (6 month Follow-up)*

38 of 109 men (35%) were considered equivocal or positive on MRI at a median of 6 months (range 154-280 days). Against initial biopsy, late MRI demonstrated greater accuracy for predicting residual tumour than early MRI, with AUROC ranging between 0.77 and 0.85 (highest for disease >3mm). As with the early MRI, the late MRI demonstrated high negative predictive values for ruling-out the presence of clinically significant tumour (86-97%) but low positive predictive values (14-44%). Specificity rates were similar across all disease categories.

Again, the additional information from subsequent positive biopsy contributed only marginally, with the greatest change observed in the positive predictive values of late MRI for ruling-in residual cancer.

<b>INITIAL BIOPSY</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>Sensitivity (%)</b>	17/27 (63%)	9/12 (75%)	8/10 (80%)	5/7 (71%)
<b>Specificity (%)</b>	60/82 (73%)	67/97 (69%)	68/99 (69%)	68/102 (67%)
<b>PPV (%)</b>	17/39 (44%)	9/39 (23%)	8/39 (21%)	5/39 (13%)
<b>NPV (%)</b>	60/70 (86%)	67/70 (96%)	68/70 (97%)	68/70 (97%)
<b>ROC (standard error)</b>	0.77 (0.054)	0.83 (0.056)	0.85 (0.053)	0.79 (0.081)
<b>ANY BIOPSY</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>Sensitivity (%)</b>	24/40 (60%)	14/21 (67%)	11/14 (79%)	9/14 (64%)
<b>Specificity (%)</b>	54/69 (78%)	63/88 (72%)	67/95 (71%)	65/95 (68%)
<b>PPV (%)</b>	24/39 (62%)	14/39 (36%)	11/39 (28%)	9/39 (23%)
<b>NPV (%)</b>	54/70 (77%)	63/70 (90%)	67/70 (96%)	65/70 (93%)
<b>ROC (standard error)</b>	0.76 (0.068)	0.78 (0.067)	0.85 (0.056)	0.72 (0.087)

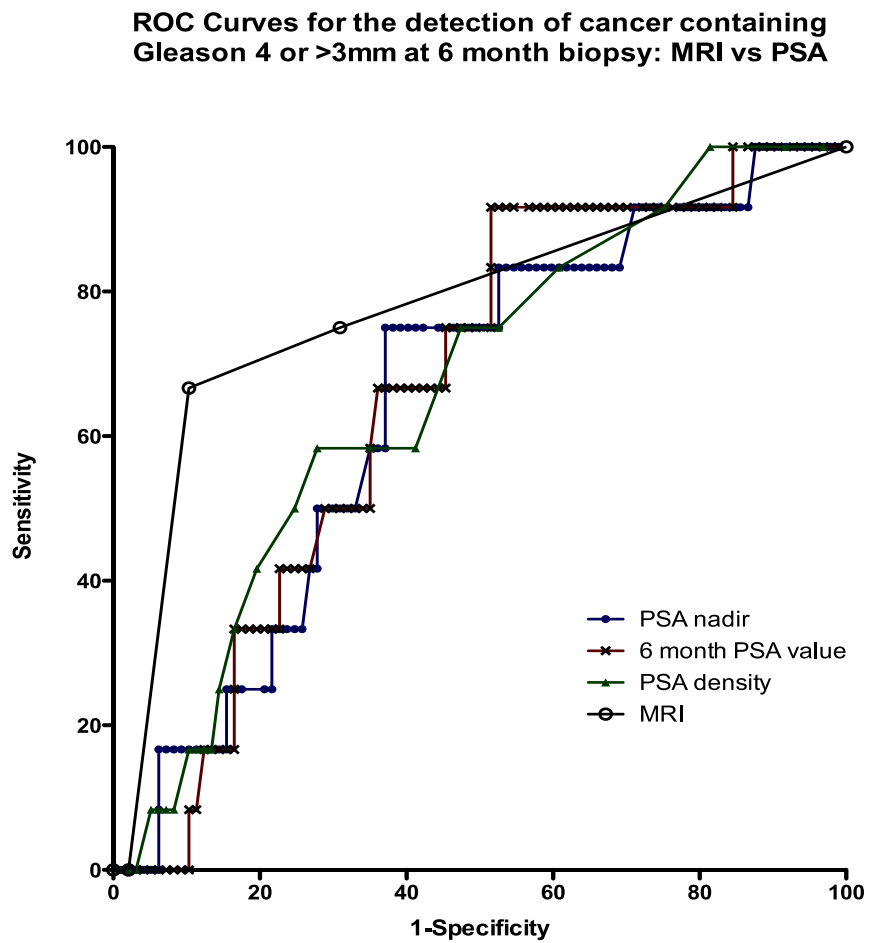
**Table 4.** Accuracy rates of late MRI against initial and subsequent biopsy

A summary of the post-operative PSA and MRI outcomes are detailed in appendix table D.

### *3.4 Statistical comparisons*

To avoid effects due to large numbers of comparisons, we restricted the statistical tests to comparing 6-month MRI with PSA criteria in a single defined group of 109

patients. In all 24 comparisons (p values given in Table 2) the AUC was higher for MRI than for PSA criteria, and in six cases the difference was statistically significant.



**Figure 2.** Fitted ROC curves comparing early and late MRI and all PSA parameters for the detection of UCL definition 2 for cancer (category 3).



#### **4. Discussion**

In this short-term study, MR imaging provided a more accurate means of detecting residual cancer than PSA biochemical parameters, against a biopsy histopathology reference standard, with high AUROC of up to 0.85 by late MRI in the detection of different criteria for clinically significant tumour.

Early and late MRI achieved very high negative predictive values, at 98% and 97%, respectively, for ruling-out the presence of residual clinically significant tumour on post-treatment biopsy. Negative predictive value in this context must be interpreted with caution, as the number of positive biopsies was low for some of the definitions of significance. The low positive predictive values achieved are likely to reflect the chosen cut-off of 3 on the Likert scale as 'positive', and threshold effects due to small tumours being classified as 'negative' for some of the definitions of significance.

Our results suggest that mpMRI is a useful test for assessing focal HIFU treatment, and in particular for confirming the absence of residual cancer in the short term.

Although the negative predictive values of the early and later MRIs are similar, the considerably higher specificity and positive predictive value of the later (6 month) scan means that it is potentially more useful.

The clinical implications extend beyond HIFU ablation, and are potentially applicable to any focal therapy. Firstly, those assessed as at high risk for under-treatment could be identified early on MRI, and closely monitored, or offered further treatment at the first appropriate opportunity. Secondly, MRI may enable a reduction in the

number of cores performed during a follow up biopsies by targeting positive areas, or a reduction in the need for post treatment biopsy if negative, although this latter application remains speculative.

By analysing accuracy rates against several definitions of residual tumour burden, we were able to show that the highest accuracy levels were achieved when identifying lesions over 3mm. The term 'clinically significant' has recently been adopted within research papers in order to differentiate between potentially indolent tumour compared to higher risk disease that is likely to warrant treatment (16-19) , although none have yet been validated. For this study we adopted several criteria of disease burden, using 3mm and Gleason 4 as thresholds of clinical significance according to UCL criteria 2 (13), not for the purpose of establishing a definition for clinical significance, but rather to assess different thresholds of volume and grade that might be predicted by either biochemical or imaging tools.

We should emphasise that the diagnostic performance of MRI in the post focal HIFU context appears potentially *better* than in the more common setting of a triage test to investigate men with a raised PSA: only 10 out of our 28 positive patients had a cancer core length >3mm, and our sensitivity of 80% for a biopsy with a CCL >3mm compares well with the finding of Villers et al of a sensitivity of 77% for lesions >0.2cc in the pre-biopsy setting (20) (a 0.2cc lesion is equivalent to a 7mm sphere, and usually returns a MCCL of >3mm (13)).

There are many limitations to this study. Whilst the cohort had all received focal therapy within three 12-month prospective studies involving protocol-mandated serum PSA, MRI and biopsies, and subsequently prospective registry data collection, our analysis included some MRI data collated in a retrospective manner, albeit blinded to the post-operative PSA and histology results.

Our analysis was performed on a heterogeneous cohort of men, with varied baseline disease burden, undergoing different focal therapy protocols. Of particular relevance, the post-operative PSA response in those men treated with ablation to the index lesion and with known untreated clinically insignificant disease may have been significantly different to those without untreated lesions. However, it could be argued that all the treatment protocols adopted an 'index lesion' approach, as the complete absence of low volume, insignificant disease within the untreated prostate cannot be fully excluded on pre-operative mpMRI and transperineal template mapping biopsies.

All of the focal therapy studies included were initiated prior to contemporary consensus statements of patient eligibility and follow-up criteria (21). As men received the first post-operative biopsy within a relatively short follow-up period (averaging just over 7 months from treatment), biopsy may not have accurately targeted and sampled any small residual lesions, potentially introducing sampling bias. It was in order to capture such cases that we included subsequent biopsy results, although with no significant effect identified on the PSA and MRI performance characteristics.

Finally, the MRI protocol changed at our institution over the study period of 6 years. While the majority of patients underwent 1.5T scans involving just T2 and dynamically enhanced sequences, some had 3T scans and others also underwent diffusion-weighted scans. Both of these are likely to improve performance (with some data on diffusion existing in the post treatment context (22)), so that we may be underestimating the potential performance of modern MRI.

## **5. Conclusions**

Whilst clinical guidance now exists on the most accurate means of localising and identifying disease to plan and conduct focal treatment, our understanding of how men receiving focal therapy are most appropriately followed up remains limited. This small, short-term study provides a first step to reducing that uncertainty. We have shown that MR imaging, in the form of early and later mpMRI, strongly predicts a negative biopsy after focal therapy for localised prostate cancer, whilst PSA parameters are less reliable.

## References

1. Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: A phase I/II trial. *J Urol* 2011, Apr;185(4):1246-54.
2. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: A prospective development study. *Lancet Oncol* 2012, Jun;13(6):622-32.
3. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, et al. Focal ablation targeted to the index lesion in multifocal localised prostate cancer: A prospective development study. *Eur Urol* 2015, Dec;68(6):927-36.
4. Bahn D, de Castro Abreu AL, Gill IS, Hung AJ, Silverman P, Gross ME, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. *Eur Urol* 2012, Jul;62(1):55-63.
5. Valerio M, Stricker PD, Ahmed HU, Dickinson L, Ponsky L, Shnier R, et al. Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. *Prostate Cancer Prostatic Dis* 2014, Dec;17(4):343-7.
6. Azzouzi A-R, Barret E, Moore CM, Villers A, Allen C, Scherz A, et al. TOOKAD<sup>®</sup> soluble vascular-targeted photodynamic (VTP) therapy: Determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer. *BJU Int* 2013, Oct;112(6):766-74.
7. Valerio M, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, et al. The role of focal therapy in the management of localised prostate cancer: A systematic review. *Eur Urol* 2013, Jun 6.

8. Barret E, Harvey-Bryan K-A, Sanchez-Salas R, Rozet F, Galiano M, Cathelineau X. How to diagnose and treat focal therapy failure and recurrence? *Curr Opin Urol* 2014, May;24(3):241-6.
9. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. *Eur Urol* 2013, Jun 4.
10. Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. *Eur Urol* 2013, Jan;63(1):125-40.
11. Punwani S, Emberton M, Walkden M, Sohaib A, Freeman A, Ahmed H, et al. Prostatic cancer surveillance following whole-gland high-intensity focused ultrasound: Comparison of MRI and prostate-specific antigen for detection of residual or recurrent disease. *Br J Radiol* 2012, Jun;85(1014):720-8.
12. Kirkham APS, Emberton M, Hoh IM, Illing RO, Freeman AA, Allen C. MR imaging of prostate after treatment with high-intensity focused ultrasound. *Radiology* 2008, Mar;246(3):833-44.
13. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. *J Urol* 2011, Aug;186(2):458-64.
14. Eng J. ROC analysis: Web-based calculator for ROC curves. Baltimore: Johns Hopkins University 2006.
15. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983, Sep;148(3):839-43.

16. Ahmed HU, Arya M, Freeman A, Emberton M. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? *Eur Urol* 2012, Nov;13(11):e509-17.
17. Ploussard G, Epstein JI, Montironi R, Carroll PR, Wirth M, Grimm M-O, et al. The contemporary concept of significant versus insignificant prostate cancer. *Eur Urol* 2011, Aug;60(2):291-303.
18. Carter HB, Partin AW, Walsh PC, Trock BJ, Veltri RW, Nelson WG, et al. Gleason score 6 adenocarcinoma: Should it be labeled as cancer? *J Clin Oncol* 2012, Dec 10;30(35):4294-6.
19. Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittemore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer* 1993, Feb 1;71(3 Suppl):933-8.
20. Villers A, Puech P, Mouton D, Leroy X, Ballereau C, Lemaitre L. Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: Correlation with radical prostatectomy findings. *J Urol* 2006, Dec;176(6 Pt 1):2432-7.
21. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes - a report from a consensus meeting. *Eur Urol* 2015, Apr;67(4):771-7.
22. Kim CK, Park BK, Lee HM. Prediction of locally recurrent prostate cancer after radiation therapy: Incremental value of 3T diffusion-weighted MRI. *J Magn Reson Imaging* 2009, Feb;29(2):391-7.

Early post HIFU MRI sequence protocol								
	TR	TE	Flip angle/ degrees	Plane	Slice thickness (gap)	Matrix size	Field of view /mm	Time for scan
<b>T2 TSE</b>	5170	92	180	axial	3mm (10% gap)	256x 256	180 x 180	3m 54s each
<b>T1 TSE</b>	502	15	150	axial	3mm (10% gap)	256 x 256	200 x 200	2m 44s
<b>VIBE with fat sat</b>	5.61	2.52	15	axial	3mm (20% gap)	192x 192	260 x 260	≥7m (sequential 16s acquisitions)
<b>T1 post contrast fat sat</b>	461	19	150	Axial, coronal	3mm (10% gap)	256 x 256	200 x 200	4m 39s each
Late post HIFU MRI sequence protocol								
	TR	TE	Flip angle/ degrees	Plane	Slice thickness (gap)	Matrix size	Field of view /mm	Time for scan
<b>T2 TSE</b>	5170	92	180	axial, coronal	3mm (10% gap)	256x 256	180x 180	3m 54s (ax), 4m18s (cor)
<b>VIBE with fat sat</b>	5.61	2.52	15	axial	3mm (20% gap)	192x 192	260x 260	7m at least (sequential 16s acquisitions)
<b>Diffusion b values: 0, 150, 500, 1000*</b>	2200	98		axial	5mm	172x 172	260x 260	5m 44s (16 averages)



<b>Diffusion b=1400*</b>	2200	98		axial	5mm	172 x 172	320x 320	3m 39s (32 averages)
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### Appendix

**Appendix Table A.** MRI pulse sequences at 1.5T. The parameters were similar or of slightly higher spatial resolution for scans at 3T. \* Diffusion-weighted imaging was performed in 15 patients.

<b>Age (years), mean (SD; range)</b>	62.9 (5.9; 48 – 77)
<b>Serum PSA (ng/ml), median (IQR)</b>	6.8 (5.7 – 9.4)
<b>Prostate volume (ml), median (IQR)</b>	35 (28 - 47)
<b>Type of tissue-sparing HIFU treatment/ trial</b>	
Hemi-ablation	18 (16%)
Focal ablation	40 (36%)
Index lesion ablation	53 (48%)
<b>Type of pre-treatment biopsy on which focal treatment was planned</b>	
TRUS biopsy	21 (19%)
TPM biopsy	90 (81%)
<b>Pre-treatment Gleason grade</b>	
3+3	31 (28%)
3+4	71 (64%)
4+3	9 (8%)
<b>Total cores (n), median (IQR)</b>	41 (29 – 63)
<b>Total positive cores (n), median (IQR)</b>	7 (4 – 11)
<b>Maximum cancer core length (mm), median (IQR)</b>	5 (4 – 8)

**Appendix Table B.** Baseline patient characteristics.

<b>INITIAL BIOPSY</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>PSA nadir</b>	0.065	0.037	0.087	0.26
<b>6 month PSA</b>	0.1	0.037	0.076	0.36
<b>PSA density</b>	0.13	0.063	0.054	0.98
<b>ANY BIOPSY</b>				
	<b>Any disease</b>	<b>&gt;3mm CCL or any Gleason 4</b>	<b>&gt;3mm CCL</b>	<b>Any Gleason pattern 4</b>
<b>PSA Nadir</b>	0.034	0.018	0.03	0.11
<b>6 month PSA</b>	0.033	0.018	0.043	0.066
<b>PSA density</b>	0.096	0.063	0.069	0.29

Appendix Table C. Table of p-values of PSA parameter ROC against 6-month MRI

ROC

<b>Post-treatment nadir PSA (ng/ml), median (IQR)</b>	<b>1.6 (0.8 – 2.8)</b>
<b>Post-treatment 6-month PSA (ng/ml), median (IQR)</b>	<b>2.0 (1.0 - 3.4)</b>
<b>Post-treatment PSA density (ng/ml), median (IQR)</b>	<b>4.5 (3.4 – 6.4)</b>
<b>Equivocal or positive early MRI (score 2 or 3) (number, %)</b>	<b>54/ 105 (51%)</b>
<b>Equivocal or positive late MRI (score 3, 4 or 5) (number, %)</b>	<b>38/109 (35%)</b>

Appendix Table D. **Post-operative PSA and MRI outcomes**