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Detection, localisation and characterisation of prostate cancer by Prostate HistoScanning™

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OBJECTIVE

- To evaluate the ability of prostate HistoScanning™ (PHS) an ultrasound (US)-based tissue characterization application, to detect cancer foci by correlating results with detailed radical prostatectomy (RP) histology.

PATIENT AND METHODS

- In all, 31 patients with organ-confined prostate cancer, diagnosed on transrectal biopsies taken using US guidance, and scheduled for RP were recruited from six European centres.
- Before RP three-dimensional (3D) US raw data for PHS analysis was obtained. Histology by Bostwick Laboratories (London) examined sections obtained from whole mounted glands cut every 3–4 mm.
- Location and volume estimation of cancer foci by PHS were undertaken using two methods; a manual method and an embedded software tool.
- In this report we evaluate data obtained from a planned open study phase. The second phase of the study is 'blinded', and currently in progress.

RESULTS

- 31 patients were eligible for this phase. Three patients were excluded from analysis due to inadequate scan acquisition and pathology violations of the standard operating procedure. One patient withdrew from the study after 3D TRUS examination.
- PHS detected cancer ≥0.20 mL in 25/27 prostates (sensitivity 93%).
- In all, 23 patients had an index focus ≥0.5 mL at pathology, of which 21 were identified as ≥0.5 mL by PHS using the manual method (sensitivity 91%) and 19 were correctly identified as ≥0.5 mL by the embedded tool (sensitivity 83%).
- In 27 patients, histological analysis found 32 cancerous foci ≥0.2 mL, located in 97 of 162 sextants. After sextant analysis, PHS showed a 90% sensitivity and 72% specificity for the localisation of lesions ≥0.2 mL within a sextant.

CONCLUSIONS

- PHS has the ability to identify and locate prostate cancer and consequently may aid in pre-treatment and pre-surgical planning.
- In men with a lesion identified, it has potential to enable improved targeting, allowing better risk stratification by obtaining more representative cores.
- However further verification from the results of the blinded phase of this study are awaited.

What's known on the subject? and What does the study add?
Prostate cancer is one of the few solid-organ cancers in which imaging is not used in the diagnostic process. Novel functional magnetic resonance imaging techniques offer promise but may not be cost-effective.

Prostate HistoScanning™ (PHS) is an ultrasound-based tissue characterisation technique that has previously shown encouraging results in the detection of clinically significant prostate cancer. The present study reports on the open 'unblinded' phase of a European multicentre study. The prospective 'blind' phase is currently in progress and will determine the value of PHS in a robust fashion overcoming many of the biases inherent in evaluating prostate imaging.

KEYWORDS

prostate cancer, diagnosis, detection, HistoScanning™

INTRODUCTION

The current prostate cancer diagnostic pathway,PSA/TRUS-guided biopsy, is unique in solid organ cancer in that no attempt is made to detect and/or locate the cancer before taking the biopsy. This means that the diagnosis of prostate cancer is based upon the chance finding of a cancer that results from a blinded examination of the prostate, a process that is subject to both systematic and random sampling error. The

result is a test that is unstable over time in terms of its cancer status. TRUS biopsy transitions from positive to negative in up to two thirds of patients on active surveillance [1], and from negative to positive in a quarter of men that are re-exposed to the test [2]. Moreover, in those men that do test positive (those in whom cancer is detected), there exists considerable imprecision in allocating men to a low-, medium- or high-risk category when the test is re-applied or when the test is compared with radical prostatectomy (RP) whole-mount pathology [3]. Clinically important discordance in risk profile has been reported in up to 50% of men [4]. It appears that at least one third of men are incorrectly classified by Gleason grade at diagnosis, and up to 50% by disease burden [4–7].

A test that could detect, localise and characterise prostate cancer at clinically meaningful thresholds might assist in reducing some of the imprecision alluded to above. The result could translate to fewer biopsies, better biopsies in those that need them and more appropriate treatment allocation to all men who receive a prostate cancer diagnosis [8].

This paper reports on the ability of prostate HistoScanning™ (PHS), an ultrasound (US)-based method for tissue characterisation that incorporates spectral analysis and pattern recognition, to detect and characterise disease by volume [9,10]. In the present report we use data obtained from a planned open-phase study that preceded a 'blinded' phase that is currently in progress.

PATIENTS AND METHODS

This registered (NCT01191931), prospective, multicentre study was approved by local Ethics Committees within the European Union [11].

Men aged >18 years with histologically confirmed, organ-confined prostate cancer, scheduled for RP and willing to undergo three-dimensional (3D) TRUS were approached for inclusion in this study. Men were ineligible if they were not scheduled for RP, had received prior treatment for prostate cancer (including any hormonal manipulation), unwilling to undergo further 3D TRUS or had large calcifications (≥5 mm) at TRUS that compromised the quality of the US signal.

Eligible men that agreed to take part and fulfilled the inclusion/exclusion criteria underwent standardised 3D TRUS acquisition with an end-fire array of a BK 8818 probe before their planned RP. Analysis of the raw (radiofrequency [RF]) back-scatter data was performed using the European Community CE marked commercially available medical device (HistoScanning™, software version 2.1, Advanced Medical Diagnostics [AMD], Belgium).

THE REFERENCE TEST

The reference test in the present study comprised a very detailed and standardised RP whole-mount step-section analysis. The RP specimens were all processed centrally by pathologists at Bostwick Laboratories, London UK. The RP specimens from the Tuebingen centre were fixed and cut at 3–4 mm intervals locally and then sent on to Bostwick laboratories for further processing.

Once 3–4 mm step sections were either performed or received by Bostwick a standard operating procedure was initiated. Subdivision of the sections was completed to full face. Any trim that was generated in achieving full face was accounted for and measured. When full face was achieved it was superimposed with a 5 × 5 mm grid. Each cell of this grid was defined as a histological region of interest and examined for the presence or absence of prostate cancer. If cancer was present the dominant Gleason pattern was recorded. The cumulative number of 5 × 5 mm cells, by incorporating rules of adjacency, that contained cancer were used to derive the 'total cancer volume' at pathology in the patient. A photograph of each section was made and the cancer contour marked in red. Placed in series these marked sections generated a 3D map, albeit at 3–4 mm intervals minus the trim.

THE INDEX TEST

PHS is an US-based tissue characterisation method that has been described previously [9,10]. From analysis of the raw backscatter data at 3D TRUS it generates binary outputs of cancer vs non-cancer.

At present, PHS is not performed in real-time during the TRUS but the 3D volume file acquired at TRUS transferred during the scan acquisition to the PHS machine, analysis can be undertaken immediately or if preferable to the clinician at a later stage.

Patients in the present study underwent preoperative 3D TRUS acquisition, performed by their treating Urologist at their local centre. All Urologists had >5 years prior experience of TRUS scanning. Experience with PHS varied amongst users most had little to no prior experience.

For the purpose of the present study, PHS analysis was undertaken centrally at the laboratories of AMD. Analysis of PHS is computer aided but requires some input from the user. The initial prostate segmentation was performed by AMD's clinical research assistant, this involves identifying using a point marker in the software the apex and the base of the prostate. The software then automatically defines a prostatic outline, which can be refined manually if needed. The PHS device then performs automated tissue characterisation sequences to identify areas suspicious for cancer, these areas are identified by red pixilation on the PHS image.

Using the embedded software tools, measurement of the suspected cancer areas was performed. The total cancer volume estimation on PHS relates to the sum of all pixels deemed to be cancerous by the embedded software tool.

A second manual estimation of abnormalities detected by PHS was performed. The manual method closely imitates that used by pathologists and by using the product of the dimensions of all the areas deemed to be cancerous by PHS, Height × Length × Depth × the coefficient of 0.52, an estimate of the volume of the lesions detected at PHS was obtained. To reduce inter-observer variation this task was performed exclusively by one of the authors (P.A.).

All analysis was performed using the commercially available PHS device with software version 2.1.

For further analysis the prostate was subdivide into six sectors divided using the

midline urethra as an anatomical landmark for right and left lobes. Each lobe was then further subdivided in an equidistant manner into apex, mid and basal sextants, generating six sectors in all. A sextant was deemed positive at histology if cancer was present in ≥10% of the surface pathology.

ANALYSES

The following analyses were carried out to compare the index test with the reference test.

I. Whole gland analysis: The total cancer volume as estimated by the two methods outlined above, the embedded software tool and the manual estimation of cancer volume compared with the total cancer volume as determined by the reference test, RP. Least-square linear regression was used to determine the Pearson correlation coefficient between the total cancer volume estimation at PHS and total cancer volume at Histopathology in the present study cohort.
II. Lesional analysis: The attribution of cancer foci above the volume thresholds of ≥0.5 mL and ≥0.2 mL at histopathology and the ability of PHS to detect these lesions was evaluated.
III. Sextant analysis: Was performed using standard 2 × 2 contingency tables for the presence of cancer above the given volume thresholds ≥0.5 mL and ≥0.2 mL, within a sextant at histopathology and PHS. Calculation of 95% CIs was done using the normal distribution approximation.

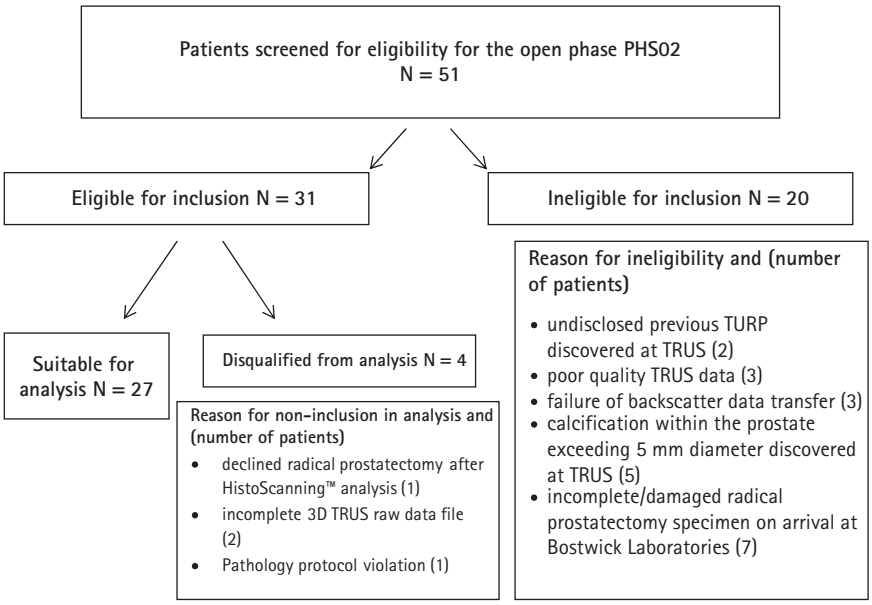
RESULTS

From 11/02/2008 to 19/03/2010, 51 patients from six European centres who were scheduled for RP were screened for recruitment to the open phase of the study. In all, 31 patients were eligible for inclusion in the study (Table 1) and 27 underwent final analysis. Figure 1 shows the flow diagram of patient enrolment to the open phase. Reasons for non-inclusion comprised: undisclosed previous TURP discovered at TRUS (two patients), poor quality TRUS data (three), failure of backscatter data transfer (three), and calcification within the prostate of >5 mm diameter discovered at TRUS (five), and/or an incomplete/damaged RP specimen on arrival at Bostwick Laboratories (seven).

TABLE 1 Eligible patient numbers according to recruiting centre

Institute	City	No. Patients
Jules Bordet Institute	Brussels, Belgium	3
University Hospital Tuebingen	Tuebingen, Germany	3
Semmelweis University	Budapest, Hungary	6
UZ-Brussels	Brussels, Belgium	3
Princess Grace	London, UK	3
Olomouc University	Olomuc, Czeck Rep.	13
Total		**31**

FIG. 1. Flow diagram of patient screening and recruitment to the open phase.



Of the 31 men that were eligible for inclusion into the study, four were excluded from final analysis. The reasons for non-inclusion in analysis are as follows: three patients were excluded because of technical issues that compromised either the reference test (a protocol violation in the histopathology procedure) or the index test (the US raw-data file was incomplete in two cases), these issues were not appreciated in the screening phase. One patient declined RP after undergoing PHS.

The mean (range) age was 63 (56–75) years and PSA level range was 2.6–26 ng/mL. The patients' characteristics are shown in Table 2.

I. Whole gland: There was a strong correlation between the total cancer volume found at pathology and the largest foci within each prostate (index lesion). Both the total cancer volume at pathology and the index lesion volumes at pathology ranged from 0.32 to 9.5 mL.

PHS found total cancer volumes ranged from 0 to 4.22 mL using the embedded volume tool and 0–6.96 mL using the manual volume method (Table 2). Pearson correlation coefficient *r* between the PHS volume estimation methods and histology was 0.72 and 0.41 for the manual estimation method and embedded volume tool, respectively Fig. 2,3.

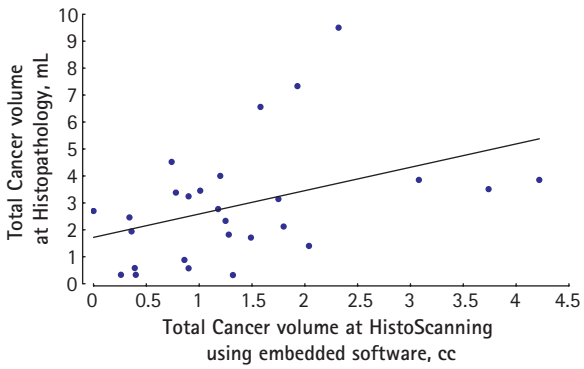
Multivariate linear regression of the analysed cases (data not shown) showed that the distance of the US compression zone, from the probe to the posterior capsule, has a large impact on the accuracy of volume estimation. Scans with compression zone distance of <3.5 mm have far better volume correlation than those

TABLE 2 Total cancer and index lesion volume at pathology and PHS

Patient ID	PSA level, ng/mL	Gleason grade at TRUS biopsy	Gleason grade at RP	Total cancer volume at Pathology, mL	Total cancer volume using PHS embedded volume tool, mL	Total cancer volume using manual PHS volume estimation, mL	Index lesion volume at pathology, mL	Index lesion volume using PHS, mL
1	6.47	3 + 4	3 + 4	3.38	0.78	1.68	2.92	0.42
2	3.3	3 + 3	3 + 4	2.12	1.8	1.63	1.45	1.77
3	4.28	3 + 4	3 + 4	0.88	0.86	0.94	0.88	0.52
4	5.13	4 + 3	3 + 4	2.46	0.34	0.96	2.46	0.22
5	10.2	3 + 3	4 + 3	3.85	3.08	6.96	3.85	2.43
6	7.9	4 + 5	3 + 4	3.85	4.22	2.83	2.25	4.17
7	21	3 + 3	3 + 4	9.5	2.32	5.28	9.5	2.25
8	18.2	3 + 3	4 + 3	2.33	1.25	2.67	2.33	1.23
9	9.2	3 + 4	4 + 3	6.56	1.58	5.03	6.56	1.45
10	7.1	3 + 3	3 + 3	0.33	0.4	0.87	0.33	0.3
11	6	3 + 3	3 + 4	0.32	1.32	0.97	0.32	0.49
12	23.71	3 + 4	5 + 4	2.7	0	0	2.7	0
13	4.96	3 + 3	4 + 3	3.51	3.74	3.66	2.9	3.71
14	9	4 + 4	4 + 3	1.82	1.28	3.41	1.82	0.78
15	4.4	3 + 4	3 + 3	0.57	0.9	2.06	0.32	0.37
16	2.56	3 + 4	3 + 3	1.4	2.04	2.13	1.4	1.56
17	7.35	3 + 4	4 + 3	4	1.2	3.5	4	0.66
18	5.07	4 + 4	4 + 3	4.52	0.74	2.5	4.52	0.61
19	3.4	3 + 4	4 + 3	3.45	1.01	2.13	3.45	0.69
20	6.6	3 + 3	3 + 3	0.58	0.39	0.88	0.58	0.39
21	2.64	2 + 3	3 + 3	0.33	0.26	0.89	0.33	0.15
22	26.3	3 + 3	3 + 4	3.24	0.9	3.73	3.24	0.79
23	16.6	3 + 4	4 + 3	7.33	1.93	5.4	7.33	1.86
24	13.1	3 + 4	3 + 4	3.14	1.75	4.6	3.14	1.17
25	10.98	3 + 3	3 + 4	1.71	1.49	1.29	1.71	1.2
26	3.3	3 + 3	3 + 3	1.94	0.36	0.35	1.94	0.29
27	16.24	2 + 4	4 + 3	2.77	1.18	2.6	2.77	0.87

, Considered negative at PHS as embedded tool detected lesion <0.2 mL. , Lesion ≥0.5 mL at pathology detected <0.5 mL at PHS.

FIG. 2.
The correlation of total cancer volume at PHS using the embedded software and total cancer volume at histopathology.



with distances of >3.5 mm. Underestimation of the index focus volume is 1.3 mL for scans with a compression distance of <3.5 mm, increasing to 3 mL when the compression zone distance is >3.4 mm. Nine patients in the present cohort had compression zone distances of >3.4 mm.

II. Lesional analysis: The reference test identified prostate cancer foci of ≥0.5 mL in 23 of 27 patients and prostate cancer foci of ≥0.20 mL were identified in all 27 patients.

At the 0.5 mL threshold, PHS identified 21 of the 23 cancer foci of ≥0.5 mL using the manual volume method (sensitivity 91%; 95% CI 0.80–1.00), thus not identifying only two tumours found at the reference test. In all, 19 of the 23 foci of ≥0.5 mL were detected (sensitivity 83%; 95% CI 0.67–0.98) using the PHS embedded software (Table 2).

At the 0.2 mL threshold the Index test identified 25 of the 27 (sensitivity 91%; 95% CI 0.83–1.00) index foci using both the embedded tool and the manual method (Table 2).

III. The number of sextants examined for PHS vs histopathology was 162 for

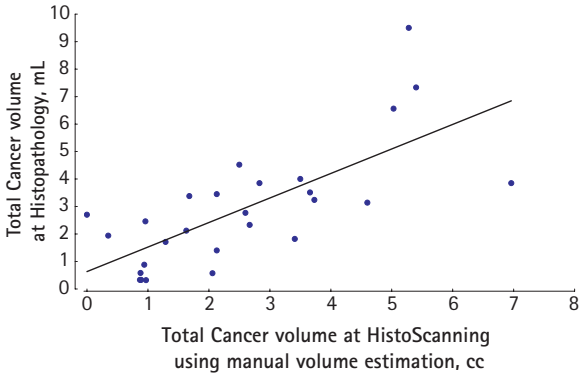


FIG. 3.
The correlation of total cancer volume at PHS using the manual volume estimation method and total cancer volume at histopathology.

TABLE 3 Sextant analysis for all 27 men. Indicating the results of the binary classification matching for the detection of cancer within a sextant at PHS (using the embedded software) vs detection of cancer within a sextant at histopathology

AREA	True positive	True negative	False positive	False negative	
1 (Right apex)	18	3	4	2	
4 (Left apex)	16	6	4	1	
2 (Right mid zone)	20	4	2	1	
5 (Left mid zone)	17	5	5	0	
3 (Right base)	10	12	0	5	
6 (Left base)	6	17	3	1	
Total no. of sextants	87	47	18	10	**162**
% of all areas	54	29	11	6	

True positive, lesion present at histology, and predicted by PHS; True negative, lesion not present at histology and not predicted by PHS; False positive, lesion predicted by PHS, but not present at histology; False negative, lesion not predicted by PHS, but present at histology.

TABLE 4 Sextant analysis of the 23 men with index focus of ≥0.5 mL at histopathology. Indicating the results of the binary classification matching for the detection of cancer within a sextant at PHS (using the embedded software) vs detection of cancer within a sextant at histopathology

AREA	True positive	True negative	False positive	False negative	
1 (Right apex)	16	2	3	2	
4 (Left apex)	14	5	3	1	
2 (Right mid zone)	18	3	2	0	
5 (Left mid zone)	16	3	4	0	
3 (Right base)	9	9	0	5	
6 (Left base)	6	13	3	1	
Total no. of sextants	79	35	15	9	**138**
% of all areas	57	25	11	07	

all 27 patients included and for the 23 patients with an index focus of ≥0.5 mL 138 sextants were examined (Tables 3 and 4).

Sextant analysis for all 27 patients with foci of ≥0.20 mL detected at histopathology (all patients in the final analysis had lesions >0.2 mL) compared with the sextant analysis of the PHS embedded software cancer volume tool showed a sensitivity of 90% and specificity of 72% for localisation within a sextant, (Table 5) negative predictive value (NPV) 82% and positive predictive value (PPV) 83% (Table 3).

TABLE 5 Sextant analysis sensitivity/specificity results for PHS at differing volume thresholds

Volume threshold for detection	≥0.20 mL	≥0.50 mL
Sensitivity, %	90	90
Specificity, %	72	70
PPV, %	83	84
NPV, %	82	80

Sextant analysis for the 23 patients with an index focus of ≥0.5 mL using the embedded software tool once again showed a 90% sensitivity and a slightly reduced 70% specificity for correct localisation of lesions of ≥0.5 mL volume within a sextant, NPV 80% and PPV 84% (Table 4).

DISCUSSION

In this open-phase prospective study we have shown that the currently available tissue characterisation algorithms within PHS software confer sensitivities in detection and localisation that approximate 90% for prostate cancer foci of ≥0.2 mL against a valid reference standard. Specificity was >70% for both detection and localisation. In other words, PHS correctly identifies nine of 10 lesions at the given thresholds. At the same time, for foci of ≥0.2 mL, it attributes a cancer in a location that is not confirmed by the reference test in one of three men who undergo the test.

Volume estimation in the present cohort shows poor correlation with underestimation in several cases. Multivariate regression showed that the distance of the US compression zone, form probe to posterior capsule, has an impact on the accuracy of volume estimation.

Before considering the clinical implications of the present findings it is important to address some of the methodological limitations associated with this study.

The first methodological limitation relates to the 'unblinded' nature of the study. This was a necessary and planned run-in to the 'blinded' phase that will serve as a verification study to this exploratory phase reported here. The unblinded phase was

important in ensuring that the standard operating procedures associated with both index and reference tests were both reliable and valid. As part of the quality control to ensure that validity and reliability were at acceptable levels some unblinding had to occur. This was, however, limited to individuals on a need to know basis. However, because of this we cannot be sure that bias was not introduced into either the reference test or, more importantly, the index test as a result of this requirement. As such this aspect of our conduct of this phase of the study does not conform to the Standards for Reporting of Diagnostic Accuracy (STARD) criteria [12]. Having said this, for the purposes of the analyses within the present report we took all measures possible to ensure that the individuals handling the data, undertaking the analyses and preparing the manuscript were not party to the unblinding.

The second methodological limitation relates to the reference test used. One of the main problems with RP specimens is that they all contain prostate cancer. This is not necessarily the case in men in whom the index test will be applied in the future. There is a danger therefore that in terms of PPV and sensitivity any test may be seen to over-perform when compared against RP. In addition, specificity cannot be correctly estimated because compared with the general population, fewer gland areas have no cancer. To mitigate this effect we undertook a per-sector analysis in which most sectors were free of prostate cancer. In the future we will need to undertake a validation of PHS with a reference test that can be applied to the target population, currently the best we have is template prostate mapping using a 5–10 mm sampling frame.

The third methodological limitation relates to the registration of 'predicted' cancer foci vs the 'observed' foci derived from the reference test. This remains a very real challenge, not just for PHS but for all imaging methods. RP specimens are difficult to process and suffer shrinkage, distortion and tissue loss that varies across specimens. Whilst we took every possible step to standardise this process and as a result mitigate the error, we can be sure that our attempts will have failed to confer accurate registration in all cases. The error that results from this will make the index test under-perform by generating false positives that are, in reality, misregistrations. For instance, in Table 3, the two false negative results in the right apex may represent two of the four false positive results in the left apex. The same reasoning could apply for three false negative results in the right base that could in fact be the false positive results in the left base. It is impossible to know the extent of this error but whatever it is it has been incorporated in our summary statistics.

A further issue in the present study relates to the number of patients that were excluded due to issues that compromised the 3D TRUS acquisition. The quality of US data acquired can affect accuracy of results and this is an important limitation of PHS and indeed all US-based diagnostic methods for prostate cancer.

All the operators at the centres' in the present study had >5 years of experience using TRUS in their routine practice; however, due to patient factors (excess calcification/movement/poor bowel preparation), mechanical factors (failure of RF transfer, 3D motor failure), and operator issues (inaccurate placement of prostate within US window, poor compression of prostate etc.) poor US data was acquired in several cases leading to ineligibility for the study or non-inclusion in the analysis. For the translation of PHS and other US diagnostic methods into routine clinical practice, it is important that the issue of the US learning curve and training amongst urologist be addressed. The Royal college of Radiology suggest in their guidelines for US training for medical and surgical specialties that for level two competence, 600 US examinations are performed under supervision [13], this will need consideration when implementing the wider use of US-based diagnostic methods.

The finding that PHS was shown to underestimate tumour volume in several patients in the present cohort, and the multivariate analysis showing the impact of a suboptimal sized compression zone, reiterates the requirement for US competence amongst operatives of this technology, and an awareness of the effects of optimum TRUS scanning requirements for best performance of the technology.

Despite the limitations we have described above, we think these results to be both important and of relevance to the current diagnostic pathway. A test with a high NPV may be of use in reassuring men that they can safely defer a biopsy. There is general agreement that we biopsy many men unnecessarily. A test that could reassure a man that he was 90% likely to be free of clinically important prostate cancer (currently much greater reassurance than is conferred by a negative TRUS-guided biopsy) is likely to be of value [14].

A test of high sensitivity or PPV could be used to assist in targeting biopsy. Much of the poor performance of our current diagnostic strategy relates to the imprecision of TRUS biopsy. Having a target to examine would place prostate cancer in line with all other solid organ cancers and may increase the accuracy of biopsy and also allow us to use fewer samples. Also, having the target information generated from an US output renders some of the cross platform (MRI to US) registration challenges redundant [15].

However, an issue to consider when thinking about the implementation of PHS to improve target generation is that currently PHS is performed, not in real-time but after 3D TRUS data file acquisition. The use of PHS in its current form to inform biopsy location requires a level of cognitive registration from the processed PHS image to the B-mode grey scale US image used by most Urologists for biopsy. Work is underway to improve the method to support real-time usage.

Whilst further work is needed to address the reliability and the responsiveness of PHS, when re-applied to an individual it is likely in its current form that it can offer material advantages to active surveillance strategies, both in case selection and in determining whether or not progression has occurred [16].

Looking a little more into the future, it seems likely that target generation such as that shown in the results presented may form the target around which tissue-preserving therapies are planned.

Much interest has been placed in the research into MRI for prostate cancer detection and the results so far are very

promising. A study by Villers *et al.* [17], comparing dynamic contrast-enhanced MRI to RP step-sectioned histopathology, showed 77% sensitivity for detection of foci of >0.2 mL with an 85% NPV. Cornud *et al.* [18] also recently evaluated the ability of multi-parametric MRI (mp-MRI) to detect and localise cancer showing a sensitivity for detection of >0.2 mL lesion of 80% and specificity 97%. The widespread clinical use of mp-MRI in the prostate cancer detection pathway and for biopsy planning may however prove problematic, due to its high cost. The practicalities for real-time MRI targeted biopsy also remain difficult with the need for specialist equipment and expertise. A review of optimal staging methods in prostate cancer concluded regarding MRI that 'With the relative cost of other clinical screening tests, using MRI as a staging examination for prostate cancer can be justified in only a small percentage of patients with high-risk prostate cancer' [19].

Considerable utility could be derived from a simple US-based method that can easily be performed in clinic and produces compcarable results to MRI. Several US derivatives are undergoing evaluation at present including contrast-enhanced TRUS and elastography. Recent data regarding contrast-enhanced TRUS [20] show that although achieving better sensitivity and specificity than standard B-mode TRUS, it fails to match that demonstrated by both PHS and mp-MRI. Elastography too has shown promising abilities in the detection of cancer with a recent review article reporting several studies showing 74–75% sensitivity and NPV 59% when compared with whole-mount pathology specimens [21]. However, elastography is currently performed only in 2D standard B-mode TRUS and thus may be of limited value in biopsy targeting and treatment planning for focal therapies.

The results from the open phase of this study have shown that PHS has the potential to benefit the prostate cancer detection and staging pathway, with increased cancer detection and tumour localisation; however, further verification of PHS ability is required in a larger cohort. The results from the 'blind' phase of this study will aid in this.

Further study is also required to assess the reproducibility of this method over successive scans and also the inter-observer variation of reporting. Also work regarding PHS target generation as real-time imaging is awaited.

Another component of vital importance in the risk stratification of prostate cancer is the accurate prediction of the aggressiveness and thus the correlation of the PHS signal with Gleason grade is another area currently undergoing investigation.

In conclusion, in the analysis of the open phase of this study, PHS has shown the ability to identify and locate prostate cancer foci. It may consequently aid in the planning of diagnostic biopsies, and different treatment methods.

In men with a lesion identified, it has the potential to improve targeting of biopsies, enabling better risk stratification by obtaining more representative cores.

PHS may also have a role in identifying men without clinically significant cancer. However, further verification is required, the results are awaited from the prospective 'blind' phase of this study that is underway.

AUTHOR CONTRIBUTIONS

L.A.M.S. was involved in data analysis and writing and review of the manuscript, including production of the first draft.

P.A. was involved in study design, data analysis, construction and review of the manuscript.

F.Z., J.B., A.P., I.R. and A.S. were all involved in patient recruitment.

K.T. and T.W. of Bostwick Laboratories were responsible for the processing and analysis of all histopathology data.

D.N. was involved in study concept and design.

C.M.M. was involved in revision of the written manuscript.

M.E. is Chief Investigator in the study described in this paper, and was involved in all aspects of study concept, design, analysis and production of the manuscript.

CONFLICT OF INTEREST

Lucy A.M. Simmons is a clinical research fellow at University College Hospital London. AMD provides supportive funding for this position.

Mark Emberton is in part funded by the National Institute for Health Research University College London Hospitals/ University College London Comprehensive Biomedical Research Centre. Mark Emberton is Chief Investigator in the study described in this paper. He also acts as a consultant to AMD. For the latter he receives no payment but does hold share options.

In addition, Mark Emberton receives research funding from Steba Biotech (Paris, France) manufacturers of TOOKAD, a photodynamic agent used in prostate cancer therapy.

Mark Emberton is a Director of Mediwatch PLC (Rugby, UK) and Prostate Mapping Ltd (Bristol, UK).

Caroline M. Moore is a consultant to Steba Biotech.

Caroline M. Moore and Mark Emberton have received travel grants for conferences and medical advisory fees from Steba Biotech.

Philippe Autier is a consultant at the International Prevention Research Institute, which receives funding from AMD for his consultancy work.

Dror Nir is Chief Executive Officer of AMD.

All other authors report no conflicts of interest.

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Abbreviations: **PHS**, prostate HistoScanning™; **US**, ultrasound/ultrasonography; **RP**, radical prostatectomy; **3D**, three-dimensional; **RF**, radiofrequency; **NPV**, negative predictive value; **PPV**, positive predictive value; **mp-MRI**, multi-parametric MRI; **AMD**, Advanced Medical Diagnostics.