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Prostate Histoscanning in Clinically Localized Biopsy Proven Prostate Cancer: An Accuracy Study

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Abstract

Purpose: To assess the accuracy of prostate histoscanning (PHS) for spatial detection and localization of prostate cancer (PCa).

Patients and Methods: Prospective, single center study from January to September 2012 was conducted. Inclusion criterion was biopsy confirmed PCa in patients scheduled for radical prostatectomy. In total, 98 patients were included in the study. Results of PHS were compared against whole-mount step sectioning by the Stanford technique. A lower limit of 0.1 cm^3 was used for PHS. A dedicated 12-sector form was used for spatial correlation. The urologist and pathologist were blinded for each other's results. Sensitivity, specificity, and receiver operating characteristic curves were calculated with a logistic regression model for covariates.

Results: PHS performance for detection of PCa lesions ≥ 0.1 cm^3 had sensitivity of 60%, specificity of 66%, and area under the curve (AUC) of 0.63. Posterior and anterior sectors achieved sensitivity of 77%, specificity of 39%, and 28% and 84%, respectively. The model containing PHS positivity within a given sector reached sensitivity of 73.4%, specificity of 65.7%, and AUC of 0.75. In a ogistic regression model, the performance of PHS was affected by sector location, rectal distance, index, and total cancer volume (all $P < 0.0001$) and bladder fullness ($P = 0.02$). The best PHS accuracy was present in midposterior sectors.

Conclusions: PHS has a potential for clinical practice, especially if PHS positivity within given sectors is taken into account. A trained operator is important. More studies are necessary to test different detection limits in various clinical settings, such as targeted biopsies and image guided focal therapy.

Introduction

One of the key points for the management of prostate cancer (PCa) is imaging being able to detect PCa lesions. Magnetic resonance imaging (MRI) is a commonly used modality for detection of PCa.[1] It is expensive, image acquisition takes a long time, and there is significant interobserver variability, however. Transrectal ultrasonography is fast, but it is also operator dependent and conventional grey-scale imaging is neither sensitive nor specific enough for PCa detection.[2]

Histoscanning is an ultrasound (US) based computer-aided application for tissue differentiation. It is designed to distinguish between benign and malignant tissue in solid organs. It uses one compound of US energy, the back-scattered waves—native radiofrequency data.[3] Acquired data are analyzed by a computer system with special software. Three different algorithms for discrimination between normal and malignant tissue are used.[4] So far, the histoscanning has been used for detection and localization of PCa[5] and ovarian masses.[6] Initial articles on prostate histoscanning (PHS) reported promising results but relatively small cohorts were studied.[3–5] Furthermore, there are also reports that PHS may become helpful in clinical applications, such as nerve sparing during radical prostatectomy (RP).[7]

The objective of our study was to assess the accuracy of PHS for spatial detection and localization of PCa with a lower detection limit of 0.1 cm^3. We compared PHS results against the whole-mount step-sectioning of the prostate.

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Patients and Methods

Patient selection

The study was conducted prospectively between January and September 2012. The inclusion criterion was biopsy confirmed PCa in men scheduled for robot-assisted or laparoscopic RP. The study was approved by the Institutional Review Board. All patients gave consent to the study. In total, 146 patients underwent PHS (HistoScanning™, Advanced Medical Diagnostics, Waterloo, Belgium) and subsequent RP. After exclusion of patients in the training set, with poor quality data (artifacts), and incomplete data, the final statistical analysis was performed with 98 subjects (Fig. 1). Notably, major rectal artifacts means that because of the rectal content, the prostate was not covered completely during scanning and missing "raw data" caused incomplete data in some regions. Also exclusion of the initial set of patients for whom the method was performed with insufficient experience was intentional to prevent poor quality scans entering the analysis. Patients' clinical characteristics are seen in Table 1.

Histoscanning acquisition

Examination was performed under general anesthesia before surgery with the patient in the lithotomy position. After PHS, digital rectal examination was performed. BK Pro Focus Ultraview ultrasound system with 8818 end-fire probe with ring adapter UA0512 was used. The probe was magnetically attached to a UA0513 rotation mover. It rotates from left to right with a range of 179 degrees; thus, 895 sagittal frames (1 frame per 0.2 degree) are acquired. The data are processed by the HistoScanning workstation with software version 2.3. Two ultrasound scans were performed for each patient. The better scan was used for analysis. Ultrasonography was performed by five urologists. Scans with artifacts generated by rectal content were excluded. The volume of interest, i.e., prostate volume, was created by embedded software with operator interaction. Highlighted lesions were reviewed on the screen and manual adjustment was performed, if necessary. All lesions $\geq 0.1\,cm^3$ were considered for analysis, because this is the minimal volume highlighted by the software. After PHS analysis, a computer generated report was created.

Table 1. Clinical Characteristics of Patients Undergoing Prostate Histoscanning and Their Stratification Based on Gleason Scoring and Local Extent

	Median (IQR)
Age	63 (60–66)
PSA (ng/mL)	6.4 (5.2–8.5)
Biopsy Gleason score	7 (6–7)
Biopsy Gleason score (GS) (in categories)	N (%)
- Low (GS ≤6)	46 (46.9)
- Intermediate (GS 7)	48 (49)
- High (GS ≥8)	4 (4.1)
Clinical T category	N (%)
- T_{1c}	54 (55.1)
- T_{2a}	29 (29.6)
- T_{2b}	9 (9.2)
- T_{2c}	4 (4.1)
- T_{3a}	2 (2)
Pathologic Gleason score (GS) (in categories)	N (%)
- Low (GS ≤6)	13 (13.3)
- Intermediate (GS 7)	83 (84.7)
- High (GS ≥8)	2 (2)
Pathologic T category	N (%)
- pT_{2a}	1 (1)
- pT_{2b}	2 (2)
- pT_{2c}	54 (55.1)
- pT_{3a}	33 (33.7)
- pT_{3b}	8 (8.2)

IQR = interquartile range; PSA = prostate-specific antigen.

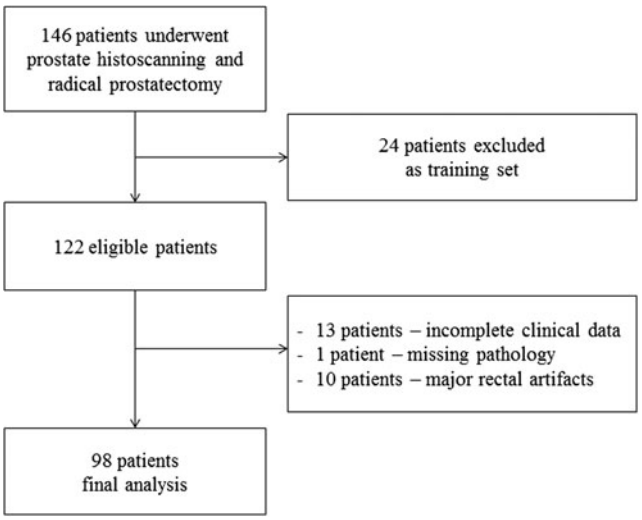

FIG. 1. Diagram showing exclusion process of patients who underwent prostate histoscanning.

Histoscanning and histology comparison

For comparison, the prostate was divided into apex, midpart, and base levels. Apex and base were defined as 1 cm from the outer margin of the prostate. Each prostate level was divided into four sectors—left and right, posterior and anterior. This made in total 12 sectors, which were drawn on a form (Fig. 2). Each patient received two copies—one for PHS analysis and one for histology. Based on the computer-generated report, the lesions were drawn into the form to depict their localization. Rectal distance (distance between the probe and posterior part of the prostate in millimeters), bladder fullness (BF) (empty = no urine; medium = bladder walls outline was completely visible, walls not touching; full = the posterior bladder wall or vertex outside the image) and scan quality (1–good, 2–average, 3–bad; based on the judgment of the operator), prostate volume, calcifications, and motion artifacts were also noted. PHS analysis was performed by one urologist. Whole-mount prostate sectioning was performed by the Stanford technique in 3 to 4 mm slices, and lesions were drawn into the form by pathologists. All histologically detected lesions were considered. The urologist and pathologist were blinded to each other's results.

Statistical analysis was performed by SAS version 9.2. Significance level of 5% was used.

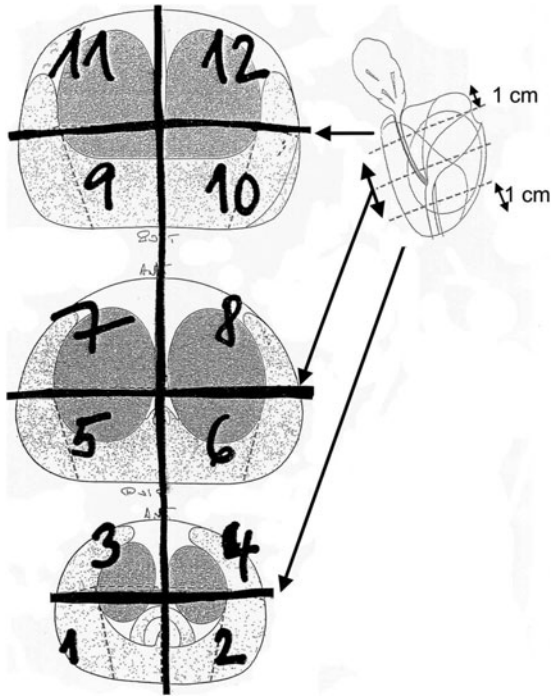

FIG. 2. The 12 sectors form for histoscanning and histology correlation.

Results

In total, 1176 sectors were analyzed. There were 523 PHS positive sectors and 473 histologically positive sectors. A complete summary of all measured variables is in Table 2.

Overall PHS performance for detection of PCa lesions of 0.1 cm^3 or greater had sensitivity of 60% and specificity of 66%, area under the curve (AUC) 0.63 (confidence interval [CI] 0.60–0.66). In the logistic regression model, the overall performance (defined as probability for positive PHS in a given area) was affected by rectal distance (RD) ($P < 0.0001$), BF ($P = 0.02$), index cancer volume (ICV) ($P < 0.0001$), total cancer volume (TCV) ($P < 0.0001$), and the sector location ($P < 0.0001$). The greatest probability of positive PHS was in all posterior sectors. PHS performance in these sectors reached sensitivity of 77% and specificity of 39%, whereas anteriorly sensitivity was 28% and specificity, 84%. The best accuracy was present in sectors 5 and 6, followed by 1, 2, 7, and 8.

Table 2. Summary of Measured Variables

	Median (IQR)	*Range*
Prostate volume (cm^3)	33 (26–47)	16–85
Number of lesions per patient	3 (2–4)	1–5
Index cancer volume (cm^3)	1.38 (0.66–2.97)	0.1–9.3
Total cancer volume (cm^3)	2.24 (1.10–4.06)	0.22–11.70
Rectal distance (millimeters)	3 (2–4)	2.8
Bladder fullness	N (%)	
- Empty	15 (15.3)	
- Medium	49 (50)	
- Full	34 (34.7)	
Scan quality	N (%)	
- Good	35 (35.7)	
- Average	57 (58.2)	
- Bad	6 (6.1)	
Artifacts	N (%)	
- None	61 (62.2)	
- Calcifications[a]	31 (31.6)	
- Motion[b]	6 (6.1)	

[a]Any calcification present.
[b]Mild motion artifacts on the periphery of the scan.
IQR = interquartile range.

PHS positivity has been inversely related to RD. The highest probability of positive PHS was in patients with medium BF and lowest for those with an empty bladder. Increasing ICV and TCV were linked with increasing probability of positive PHS (Fig. 3).

We did not observe any effect of scan quality on PHS performance, but there was a trend toward significance ($P = 0.066$). In the same model, we did not observe any effect on PHS from prostate-specific antigen (PSA) level ($P = 0.66$), clinical T category ($P = 0.29$), prostate volume ($P = 0.30$), and the presence of artifacts other than rectal ones (calcifications and motion) ($P = 0.59$).

An important observation regarding different Gleason scores (GS) was also made. The probability of PHS positivity was found to be different for biopsy GS and pathology GS stratified into categories low (GS < 7) *vs* intermediate (GS $= 7$) *vs* high (GS > 7) ($P < 0.0001$ for both) (Fig. 4). The detection rate was higher in patients with higher biopsy GS and higher final pathology GS (Fig. 4).

To find the best possible accuracy of PHS, several prediction models were analyzed. We have combined probability of positive histoscanning in a given sector, and it resulted in sensitivity of 73.4% and specificity of 65.7% with AUC of 0.75 (CI 0.72–0.78) (Fig. 5). Adding the PSA into the model changed the AUC only minimally to 0.75 (CI 0.73–0.78) with slightly lower sensitivity of 72.1% and higher specificity of 66.1%.

Discussion

PHS is one of the new US-based technologies that has become available. Currently, there is a nice pool of competing US-based modalities—color Doppler US, power Doppler US, contrast-enhanced US, real-time elastography (RTE) and shear-wave elastography.[2,8–11] Moreover, there are several technologies available that allow fusion of MR and real-time US image.[12,13] Of course, we should not forget MRI with functional modifications such as dynamic contrast enhancement, diffusion weighted MRI, MR spectroscopy as parts of a multiparametric MRI (mpMRI).[14] A comparison of various imaging modalities is difficult, however, because of the great variability of used primary end points (sensitivity, accuracy, correlation, etc.) and also the intended use (PCa detection *vs* image guidance).

For prostate lesions of 0.1 cm^3, we found that PHS achieved overall sensitivity of 60% and specificity of 66%. A model combining PHS positivity with sectors reached sensitivity of 73.4% and specificity of 65.7%. We have to view these results cautiously from a perspective of application in clinical practice. The initial report in 2008 of Braeckman and associates[3] from a small group of 14 patients comparing PHS against whole-mount prostate sectioning as well found 100% PHS concordance for detection of prostate cancer multifocality and also cancer laterality. Later that year, the similar author group

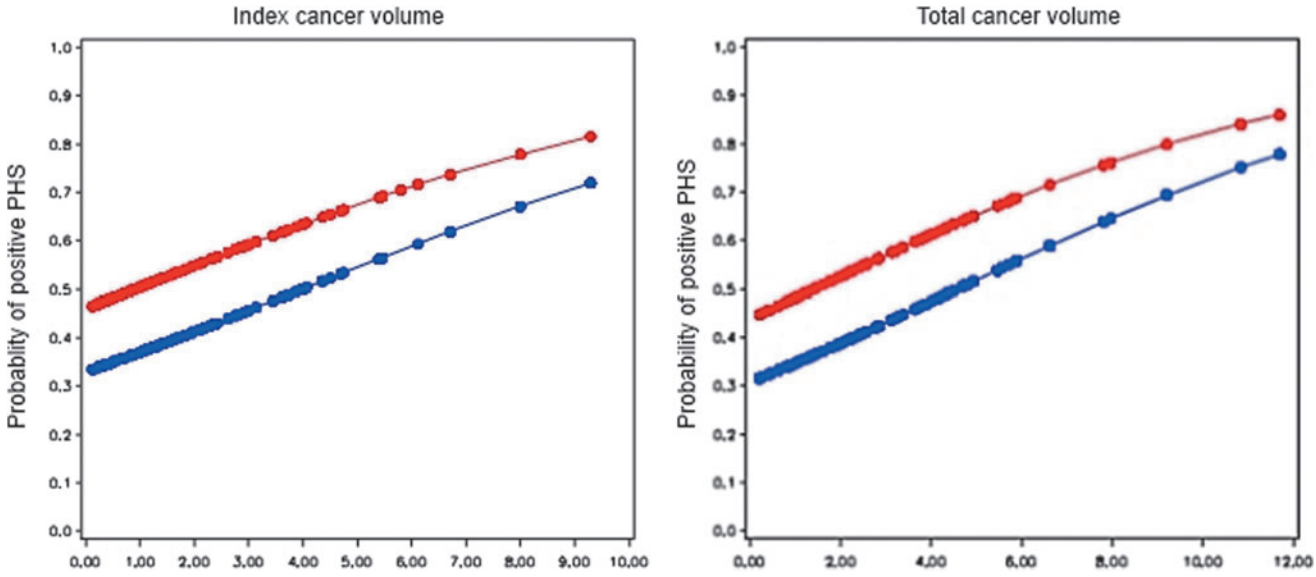

FIG. 3. The probability of positive histoscanning according to the volume of index cancer lesion (left chart) and the total cancer volume (right chart) (cm^3). Red line–sectors with positive histology; blue line–sectors with negative histology.

published 100% sensitivity of PHS (12 of 12) and specificity of 82% for detection of PCa lesions.[4] In addition, Simmons and colleagues[5] recently reported PHS sensitivity of 93% with correct detection of 25 of 27 prostate lesions.

The difference between our results and data published so far lies in the different methodology of our study. The two main factors make direct comparison with previous basically impossible: (1) The lower limit of lesion size on PHS and (2) the number of evaluated regions. So far published works of Braeckman and coworkers[3,4] were aimed at the detection of PCa lesions within the whole prostate gland or on one side only. The PHS study by Simmons and colleagues[5] had the lesion limit for statistical comparison set at 0.2 cm^3 and the reported sensitivity of 93% was related to the lesion size within the whole prostate. When compared with sextants (i.e., six regions of the prostate), the sensitivity for 0.2 cm^3 lesion was 90% and specificity 72%.[5] Our study had the minimal PHS detection limits set to 0.1 cm^3 because this is the minimal size of lesion that is color highlighted by the HistoScanning workstation software, and the prostate was divided into 12 sectors. This frequently brought on the situation that one lesion was spread over more than one sector.

Another methodologic difference was that the prostate apex and base were defined as 1 cm distance from the outer margin of the prostate outline, whereas other reports do not specify such stratification exactly and we may just suppose division into three ideal levels. The substratification of the prostate into different numbers of regions has probably the utmost significance. The publication of Salomon and associates[10] reporting the results of RTE in the detection of prostate cancer in a similar

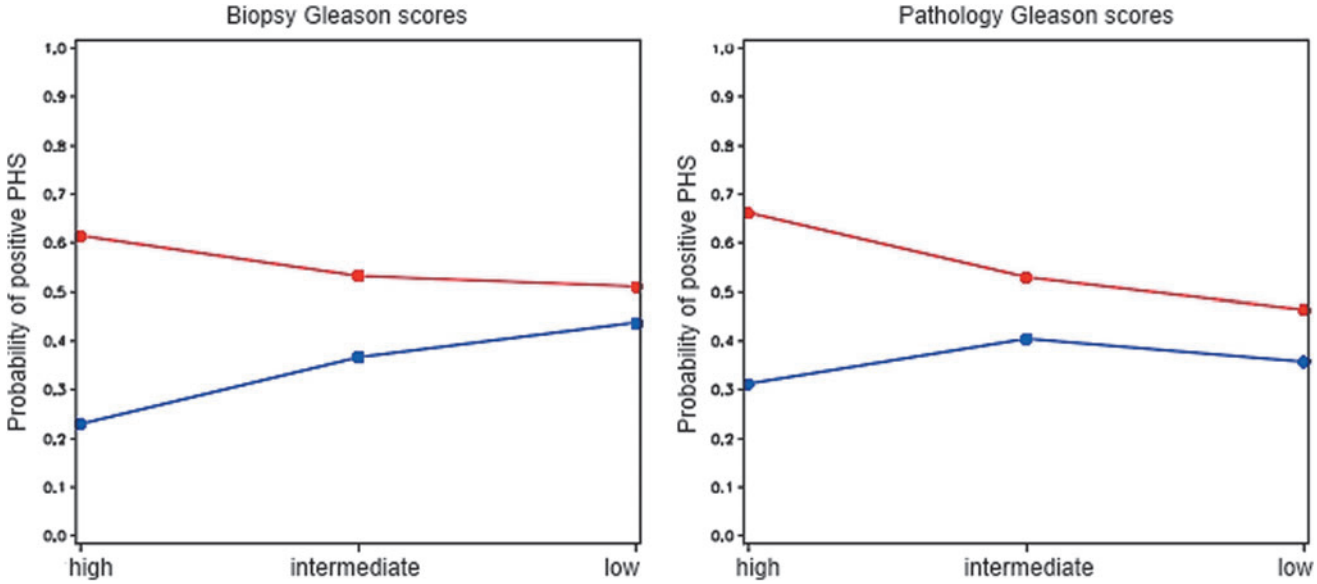

FIG. 4. Difference in the performance of prostate histoscanning according to the biopsy (left chart) and pathology (right chart) Gleason score categories ($P < 0.0001$ for all).

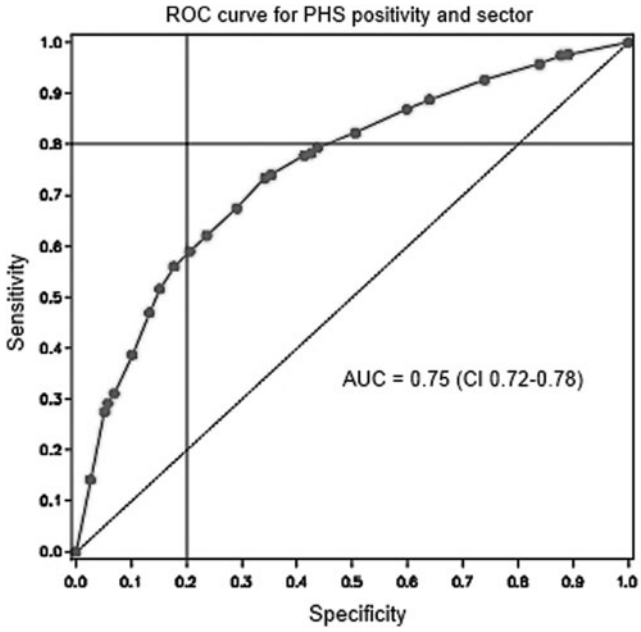

FIG. 5. Receiver operating characteristic (ROC) curve for model containing prostate histoscanning (PHS) positivity and sectors. AUC = area under the curve.

setting (comparison against whole-mount specimen sectioning) indicates sensitivity 75.4% and specificity 76.6% at the sextants level. The same US modality on 12 regions reached sensitivity of 73.4% and specificity of 79%.[15] When mpMRI was used with the prostate divided into 18 regions for analysis, average sensitivity was from 60.2% to 75.9% for index lesion defined as ≥ 1 cm.[16] If 24 regions were used, mpMRI in intermediate- and high-risk patients had sensitivity of 58.8%.[17]

The guidelines of the European Society of Urogenital Radiology recommend division of the prostate into a minimum of 16 regions plus scoring each region on a standard scale from 1 to 5.[14] It simply means, the more regions we choose to compare, the lower "accuracy" we may get.

Our approach combining PHS positivity and specific sector reached sensitivity of 73.4% and specificity of 65.7% for lesions of 0.1 cm^3 within 12 sectors. Such segmentation has a potential role in (1) targeting prostate biopsies or (2) focal therapy of prostate cancer. Others have already proven that targeted biopsies increase the detection of prostate cancer, may detect more significant cancers, and may be performed with a smaller number of biopsy cores taken in a smaller number of men. This was proven for US-based techniques,[8,18,19] for MRI/US fusion,[12,13] and also MRI only based techniques.[20] Based on the Consensus Meeting in Amsterdam, there is currently no reliable, accepted US imaging for accurate cancer characterization that would allow focal therapy.[21] Our data show promise, but larger studies need to be completed before any conclusion can be made.

The three variables models (PHS positivity, prostate sector, and PSA) did not perform better compared with the two variables model. We assume it is given by the cohort characteristics, where the majority of patients were clinically low or intermediate risk and PSA alone had no effect on PHS performance.

Our study also indicates potential limitations that US-based imaging may have. It performs significantly better in the peripheral parts of the prostate, where we achieved sensitivity of 77% with specificity of 39%. A similar observation was made with other US-based imaging.[22,23] Some may suggest that we should focus on significant PCa lesions and not be bothered with areas of 0.1 cm^3. This is only partially true, because before we say that we can forget small lesions, we have to know the exact limits of the technology we use. Here lies the potential importance of the observation that positivity of PHS seems to depend on GS, with better detection of PCa with higher GS. This may mean that even lesions smaller than 0.5 cm^3 may be significant because of the characteristics of PCa. More patients need to be analyzed for a confirmation, however. If proven, PHS may represent one of the tools for PCa patients in active surveillance (AS) protocols, because should a modality with capacity to distinguish aggressiveness of PCa be available (such as PHS), we might be potentially able to guide AS based on the number and characteristics of the lesions.

RD (distance between the probe and the posterior surface of prostate) appears to be a possible limitation of PHS. It has been proven that scans with a distance ≤ 3.5 mm have better lesion volume estimation.[5] We have made a similar observation that greater RD leads to decreased PHS performance. We did not find an effect of calcifications and motion artifacts on PHS performance. It is also unclear whether PHS can be affected by different probes. We have used the same probe (BK 8818) as Simmons and colleagues,[5] whereas Braeckman and coworkers[3,4] have used probes 8665 and 8658. Varying prostate coverage by different probes (end firing *vs* side firing) may have an effect on the completeness or quality of the scans with resulting difference in histoscanning results. Unfortunately, no direct comparison is currently possible.

We have not proven that scan quality (SQ) had an effect on the overall performance. One of possible explanations is a selection bias, because we included the better of the two scans acquired. Interestingly, we found that the BF affected the results. It seems that if the bladder is completely empty, it decreases the chance of correct prostate base visualization with subsequent risk of incorrect tissue characterization. This may be an explanation for results achieved in all sectors of base. The data on BF, SQ, and RD are important for planning of future studies to optimize PHS data acquisition.

Conclusion

This single center prospective study of PHS performance in unselected (no prostate conditions excluded) patients with so far the largest cohort of 98 subjects indicates some potential. PHS is able to detect prostate cancer foci of 0.1 cm^3 and localize it with overall sensitivity of 60% and specificity of 66%, and when extrapolated to sectors in midgland and posterior apical sectors, it is 73.4% and 65.7%, respectively. These results are not very high, but certainly set ground for further research in different settings, such as fewer regions or with a higher lower limit of cancer lesion detected. Nevertheless, it is difficult to make any comparison with the previous studies on PHS or even other US-based prostate imaging because of the inconsistency in defined end points, number of regions assessed, and their definition. Therefore, further studies are necessary with testing the PHS performance for targeted biopsies and image-guided treatment, such as focal therapy.

Our study also identified technical points necessary to focus on during scan acquisition to receive reliable data. To

achieve "optimal conditions" we recommend: Keeping the distance between the probe surface and the prostate at 3 to 4 mm, having medium BF (instruction to patient is necessary), and avoidance of any rectal content to achieve optimal initial scan covering all parts of it.

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Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

AS = active surveillance
AUC = area under the curve
BF = bladder fullness
GS = Gleason score
ICV = index cancer volume
mpMRI = multiparametric magnetic resonance imaging
MRI = magnetic resonance imaging
PCa = prostate cancer
PHS = prostate histoscanning
PSA = prostate-specific antigen
RD = rectal distance
RP = radical prostatectomy
RTE = real-time elastography
SQ = scan quality
TCV = total cancer volume
US = ultrasound