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ORIGINAL ARTICLE

Prostate 3D ultrasound-guided imaging device (HistoScanning) performance detecting clinically significant prostate cancer

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The work was done in National Cancer Institute.

Summary

Purpose: *This is a prospective pair cohort validating study to assess the clinical performance of a 3D ultrasound-guided imaging device (HistoScanning) to detect clinically significant prostate cancer.*

Methods: *Data was collected prospectively from April 2016 to September 2018 from 200 patients who had their serum PSA levels rising for at least 4 months after previous negative trans rectal ultrasound-guided TRUS biopsy in a single center. All eligible men underwent prostate HistoScanning (PHS) and transperineal template prostate mapping biopsy as our reference standard and additional single targeted biopsy, when PHS device tested positive with a suspicious lesion of ≥0.5 cm^3. Our primary goal was to obtain the results of PHS ability to detect clinically significant prostate cancer. Our secondary goal was to acquire data on PHS targeted biopsies.*

Results: *In our study 200 men were enrolled and their mean age was 62 ±5.9 years. The mean number of previous biopsies was 1.51±0.65. The mean volume for PHS index lesion in any one prostate was 1.56 ±2.01 ml. Clinically significant prostate cancer (csPCa) was detected in 41 (20.5%) patients on biopsy. Sensitivity of PHS for detecting csPCa was 61.9% (95% CI 45.64-76.43) with specificity 27.85% (95% CI 21-35.53). Positive predictive value (PPV) and negative predictive value (NPV) for PHS were 18.57% (95% CI 15-22.76) and 73.33% (95% CI 63.45-81.33), respectively. Overall accuracy calculated by AUROC curve was 0.39 (95% CI 0.3-0.47).*

Conclusion: *PHS performance results of our study on detecting clinically significant prostate cancer were insufficient to include this ultrasound-guided diagnostic test as standard diagnostic tool.*

Key words: *histoscanning, prostate cancer, targeted biopsies, transperineal template mapping biopsy*

Introduction

Detection of clinically significant prostate cancer (csPCa) remains challenging. At the time, the key test for diagnosing csPCa is systematic transrectal ultrasound-guided (TRUS) prostate biopsy. However, TRUS biopsy show up to 30% false negative rate, doesn't reflect the volume of csPCa lesions and often misclassifies the Gleason grade of the cancer [1]. Patients after previous negative biopsy results and their serum PSA levels rising may be offered a repeated biopsy, with subsequent higher rates of complications as well as higher costs [2]. Recently published data of a large multicentre, randomized, prospective study showed MRI-targeted biopsies were superior to standard TRUS biopsy in men with clinical suspicion of prostate cancer [3]. Furthermore, some devices of MRI-TRUS fusion image-guided prostate biopsy have become available. A prospective analysis of 240 patients

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showed high accuracy results for MRI-TRUS fusion image-guided prostate targeted biopsies with the AUC 0.835 [4]. Even though MRI-assisted biopsy techniques are proving their superiority over pure ultrasound, specialists are still sceptical about MRI accessibility and cost-effectiveness for routine diagnostic use. Urologists are in need of new routine diagnostic tests to improve diagnostics of csPCa and reduce the number of unnecessary biopsies and related complications. Prostate HistoScanning (PHS) is a modern 3D ultrasound imaging device that helps the physician detect clinically significant prostate cancer lesions [5]. Although the first articles showed high accuracy (>90%) [6,7], the latest published data was contradictory. A retrospective analysis of 198 biopsies was published with sensitivity and specificity of 40.1% and 73.3%, respectively [8]. Another prospective analysis showed even lower accuracy results with the AUC of only 0.43-0.47, depending on the selected index lesion area size [9]. Therefore, we present our data of a prospective, cohort validating trial to evaluate PHS diagnostic value.

Methods

Data was collected prospectively from April 2016 to September 2018 from 200 patients who had their serum PSA levels rising for at least 4 months after previous negative TRUS biopsy in a single center of National Cancer Institute of Vilnius, Lithuania. All men signed informed consent for their inclusion in the trial. All eligible men underwent PHS, which was analyzed by a team of radiologists and urologists. During the procedure the analyst defines the contours of the prostate and the software analyses the ultrasound voxels to deem the likelihood of containing malignant tissue using algorithms. PHS criterion for the prediction of a positive biopsy was a positive PHS signal of ≥0.5 cm^3 volume in the corresponding area. After completing PHS procedure, all men underwent 20-core-transperineal template mapping biopsy (TTPM) which was performed by a single urologist. After completing 20-core-TTPM biopsy, men with PHS lesions ≥0.5 cm^3 had additional targeted biopsies taken visually directed to the largest lesion in the prostate. The procedure was performed under general anesthesia with antibiotic prophylaxis and patients in lithotomy position. All patients had their biopsy specimens evaluated at the State Pathology Center, branch of Vilnius University center. The histological reporting followed the scheme of interpreting the Gleason grading. Disease significance was defined on biopsy by primary definition of the presence of Gleason ≥4+3 or a maximum cancer core length ≥6 mm in one location or a total cancer core length ≥10 mm in all locations [10].

Subanalysis was performed to evaluate outcomes for the group of small/medium sized prostate (≤ 60 cm^3) and the group of large prostates (> 60 cm^3).

Statistics

Descriptive statistics were used to summarize patient characteristics (Age, PSA, prostatic volume). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with binomial 95% confidence interval (CI). Overall accuracy was calculated using area under receiver operating characteristic (AUROC) curves (Figure 1).

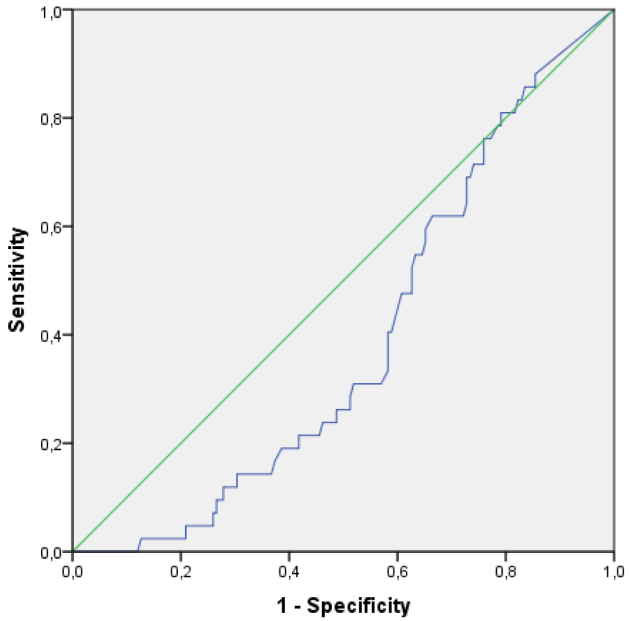

Figure 1. Area under receiver operating characteristic (AUROC) curve of prostate HistoScanning on diagnosing clinically significant prostate cancer. Diagonal segments are produced by ties.

Table 1. Patient demographics

Demographics	*Median (mean, SD, range)*
Age, years	62 (62.13, 5.9, 46-75)
PSA concentration at consent, ng/ml	4.8 (5.63, 2,86, 1.66-21)
	Mean (SD)
No. of previous biopsies	1.51 (0.65)
TRUS prostate volume, cm^3	69.07 (41.17)

Table 2. Histopathological findings after TTPM biopsy

Biopsy result	*n (%)*
Prostate tissue	19 (9,5)
Benign hyperplasia	2 (1)
Chronic prostatitis	58 (29)
HPIN	15 (7,5)
Gleason score	
3+3	80 (40)
3+4	18 (9)
4+3	7 (3,5)
4+4	1 0,5)
Total biopsies	200

Table 3. Detailed results of targeted biopsies. Benign meaning prostate tissue (benign hyperplasia, chronic prostatitis, HPIN). Insignificant meaning clinically insignificant prostate cancer. Significant meaning clinically significant prostate cancer

PHS results \ *TTMP results*	*Benign*	*Insignificant*	*Significant*	*Total*
Benign	64	41	30	135
Insignificant	1	3	0	4
Significant	2	0	3	9
Totals	67	44	33	148

Table 4. Prostate HistoScanning performance characteristics for clinically significant prostate cancer

	Sensitivity % (95% CI)	*Specificity* % (95% CI)	*PPV* % (95% CI)	*NPV* % (95% CI)	*Positive likelihood* % (95% CI)	*Negative likelihood* % (95% CI)	*AUC* % (95% CI)
PHS performance on all patients	61.9 (45.64-76.43)	27.85 (21-35.53)	18.57 (15-22.76)	73.33 (63.45-81.33)	0.86 (0.66-1.11)	1.37 (0.86-2.17)	0.39 (0.3-0.47)
Group of prostate							
≤60 cm^3	50 (31.89-68.11)	57.58 (44.79-69.66)	36.36 (26.78-47.17)	70.37 (61.33-78.05)	1.18 (0.75-1.84)	0.87 (0.58-1.30)	0.45 (0.39-.51)
>60 cm^3	20.00 (2.52-55.61)	84.78 (75.79-91.42)	12.5 (3.64-35.07)	90.7 (87.60-93.08)	1.31 (0.35-4.97)	0.94 (0.68-1.3)	0.48 (0.29-0.66)

IBM SPSS 23 version was used to perform statistical calculations with any test of p=0.05 as the threshold for statistical significance.

Results

Enrolled were 200 men with mean age 62 ±5.9 years. Mean PSA concentration was 5.63±2.86 ng/ml. Mean TRUS prostate volume was 69.07±41.17 cm^3. Mean number of previous biopsies was 1.51±0.65 (Table 1). Forty-one (20.5%) patients had clinically significant prostate cancer on biopsy. One hundred four (52%) patients had prostate cancer of any significance on biopsy. Biopsy results are presented in Table 2. Mean volume of PHS index lesion in any one prostate was 1.56±2.01 cm^3. One hundred forty eight patients underwent targeted biopsies to the largest suspicious lesion detected by PHS. One hundred sixteen (78.38%) were incorrectly classified as benign or malignant by PHS comparing to biopsy results. Thirty (73.17%) patients with csPCa biopsy results were misclassified as benign by PHS. Two (4.88 %) patients were diagnosed with csPCa by targeted biopsies on PHS suspicious lesions, when on 20-core-TTPM biopsy csPCa was undetected. Detailed results of PHS targeted biopsies are shown on Table 3. Sensitivity of PHS for detecting clinically significant prostate cancer was 61.9% (95% CI 45.64-76.43) with specificity 27.85% (95% CI 21-35.53). PPV and NPV for PHS were 18.57% (95% CI 15-22.76) and 73.33% (95% CI 63.45-81.33), respectively. Overall accuracy calculated by AUROC curve was 0.39 (95% CI 0.3-0.47; Table 3). There was no statistically significant difference of PHS performance between the groups with prostate under 60 cm^3 and over 60 cm^3. PHS performance characteristics for csPCa of groups with prostate under 60 cm^3 and over 60 cm^3 are shown on Table 4.

Discussion

Our study supports the findings of other recently published studies with poor PHS overall accuracy performance. Javed et al compared PHS-targeted biopsies to standard TRUS-guided biopsies with disappointing results on prostate cancer detection (overall cancer detection rate of 38.1% compared with 61.9% with standard TRUS-guided biopsies) [11]. Schiffmann et al published data of the largest to date retrospective study of PHS performance for predicting positive biopsy results with area under the curve 0.58 [8]. The latest and largest prospective cohort validating study assessing PHS (PICTURE study) by Simmons et al showed that PHS has poor accuracy in patients requiring repeated biopsies (AUC=0.47 on largest suspicious area ≥0.5 cm^3) [9]. These studies support the results of our trial with AUC for detecting clinically significant prostate cancer, yielding only 0.39 which is lower than a flip of a coin (AUC

0.5). However, data in the literature have been controversial with some earlier studies showing high PHS accuracy performance characteristics detecting PCa lesions of ≥0.5 cm^3 with sensitivity and specificity up to 100% and 80%, respectively [7,12].

During the previously mentioned PICTURE study, the authors have excluded patients with larger glands for safety reasons which could have had an impact on the results. We decided to create two groups of patients dividing them to small-medium (≤ 60 cm^3) prostate and large prostate (> 60 cm^3). However, we have found no statistically significant difference between the groups with AUC (95% CI) of 0.45 (0.39-0.51) and 0.48 (0.29 - 0.66), respectively.

Finally, we compared the results of PHS with transperineal template prostate mapping (TTPM) biopsies as our reference standard. In the literature TTPM show better accuracy results and avoid many of TRUS biopsies disadvantages [13]. These technical characteristics minimises possible biases for the study results compared to TRUS.

Conclusion

Our study shows that PHS underperforms in the detection of clinically significant prostate cancer. PHS guidance for targeted prostate biopsies was inaccurate. Therefore, we do not recommend PHS as a standard diagnostic tool.

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Conflict of interests

The authors declare no conflict of interests.

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