Title:
HistoScanning™ to Detect and Characterize Prostate Cancer – A Review of Existing Literature

James S Wysock, MD, MS
Assistant Professor of Urology
Department of Urology
New York University School of Medicine
NY, NY 10016

Alex Xu
New York University School of Medicine
NY, NY 10016

Clement Orczyk, MD, PhD
Consultant Urological Surgeon
Department of Urology
University College London Hospital
Honorary Clinical Senior Lecturer
Division of Surgery and Interventional Sciences, University College London

Samir S. Taneja, MD
The James M. Neissa and Janet Riha Neissa Professor of Urologic Oncology
Professor of Urology and Radiology
Director, Division of Urologic Oncology
Department of Urology
New York University Langone Medical Center
New York, New York

Corresponding to: james.wysock@nyumc.org

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Abstract:

Introduction
The widely acknowledged limitations of the standard prostate cancer (PCa) diagnostic paradigm have provided an impetus to explore novel imaging modalities to diagnose, localize, and risk stratify PCa. As the body of literature focused on Histoscanning™(HS) grows, there is need for a comprehensive review of the clinical efficacy of this technology.

Sourcing of literature
Eighteen original, English language articles were found to adequately study the use of Histoscanning™ for prostate cancer diagnosis in the clinical setting. The articles were found by conducting a bibliographic search of PubMed in April 2017 in addition to utilizing references.

Evidence Synthesis
The studies are divided into four groups based on study design. Study methods and quantitative data are summarized for each of the relevant articles. The results are synthesized to evaluate the utility of Histoscanning™ for the purpose of diagnosing PCa.

Conclusions
Despite the promise of early pilot studies, there is a lack of consistent results across a number of further investigations of Histoscanning™. This becomes increasingly evident as study size increases. As various other modern diagnostic modalities continue to develop, the future of Histoscanning™, both alone and in conjunction with these technologies, remains unclear.

Introduction:

For men clinically suspected of harboring prostate cancer, diagnostic confirmation relies upon tissue evaluation with biopsy. Image guidance with transrectal ultrasound (TRUS) provides a cost-effective, portable, and efficient method for many urologists to perform prostate biopsy (PBx) in an outpatient fashion. Modern TRUS probes offer excellent imaging quality, enabling the urologist to accurately delineate prostate boundaries and prostate zonal anatomy. The reliability, low-cost, ease of use of TRUS biopsy has led to the proliferation of office based PBx. However, current TRUS technology does not reliably differentiate between benign and malignant prostate tissue.[1, 2] While biopsy strategies have evolved to mitigate these limitations, overall TRUS PBx performance remains hindered by a false negative rate of approximately 30-40%.[3] Inaccurate grade estimation in up to 30% further complicates the diagnostic performance of TRUS PBx. [4] Coupling the poor diagnostic capability of TRUS prostate imaging with the test characteristics of serum PSA has contributed to the over-diagnosis and overtreatment of PCa.[5]

Numerous efforts are underway to improve upon the standard prostate evaluation. Clinical genomic testing, improved PSA derived assays, and multi-parametric MRI (mpMRI) offer novel approaches to disease risk assessment with improved specificity for prostate cancer.[6] Especially important is the incorporation of mpMRI.[7, 8] As the data supporting incorporation

of mpMRI into the diagnostic paradigm continue to grow, widespread access to quality MR imaging and interpretation remains a challenge.[9, 10]

Ultimately, the diagnostic paradigm bottleneck arrives at the TRUS guided prostate biopsy. Efforts to improve TRUS diagnostic performance include contrast-enhanced ultrasound (CEUS), computer-assisted TRUS (C-TRUS), elastography and Histoscanning™.[11] Additionally, early investigations into higher resolution TRUS probes have been reported.[12] These varying techniques aim to partner with the existing equipment employed by most urologists and thus augment diagnostic performance at the point of biopsy. Furthermore, imaging to guide biopsy offers the possibility to define a target in three dimensions and thus more accurately localize disease.[13]

Introduction to Histoscanning ™

Histoscanning™ is a novel diagnostic method for evaluating prostate tissue using ultrasound backscatter information to provide feedback on cancer localization, tumor volume and assessment of extraprostatic extension (EPE).

Physics of the backscatter signal

Conventional TRUS images are collected by tracking the wave front of an ultrasonic pulse and the signals echoing from tissue boundaries. Results are typically displayed in B-mode imaging, in which brightness is correlated to the intensity of echo from a particular macroscopic region of the prostate. However, microscopic echoes known as ultrasound backscatter are also collected but omitted from the ultrasound display in order to create a clearer image for prostate anatomy definition.[14]

Backscatter properties of malignant or other suspicious tissue vary from that of normal prostatic tissue in characteristics such as cell density, irregular growth patterns, water content, vascularization, elasticity, and invasion into blood or lymphatic vessels.[14, 15] While not sufficient to determine precise prostate histology, unfiltered backscatter is used by HS to identify and assess areas suspicious for PCa.[14]

Calibration of backscatter signal for detection of prostate cancer

The large amount of data produced during image acquisition, the backscatter signal, must be calibrated for the purpose of identifying signals associated with cancer. Histoscanning™ proposes three different algorithms linked to vascularity, tissue heterogeneity and cell density to analyze the signals before displaying the results to the screen. The designation of abnormal tissue is based upon an initial training set of HS imaging. This training set of data was correlated with whole mount radical prostatectomy specimens.[16]

Mechanics of Histoscanning ™ acquisition process

Histoscanning™ begins with collection of a continuous set of ultrasound data comprised of raw or native radio-frequency signals acquired from a high-resolution ultrasound scanner.[14] The entire prostate gland is scanned in order to create a 3D TRUS image. In order to ensure that

imaging data is accurately collected, the ultrasound probe is connected to an external motor that sweeps the TRUS probe sagittal array in a precise 360 degree sweep.[14, 17] The prostate gland is then segmented in the software platform by the physician. The software then applies the HS algorithm to the defined prostate region and divides this region into small sub-volumes referred to as “tagged units”. The backscatter signal is analyzed from each tagged unit. The software then categorizes each tagged unit as suspicious or non-suspicious, generating a red overlay for areas suspicious for PCa. Any area of low-quality imaging data displays a purple overlay.[14]

Histoscanning ™ True Targeting & Perineal Histoscanning ™ Targeted Biopsy

In a similar manner to MRI-US fusion approaches, Histoscanning™ True Targeting (PHS-TT) allows for conversion of HS results to real-time TRUS targets.[18] Following acquisition of HS imaging and analysis, an additional software tool provides the operator with feedback and instructions on how to maneuver the TRUS probe fitted with a needle guide in order to sample cores from specific areas of suspicion that have been identified.[4]

Perineal Histoscanning-guided biopsy is performed with the patient in dorsal lithotomy position under general or spinal anesthesia. Using the HS report and a brachytherapy template grid as guides, the biopsy needed is directly guided by triplane ultrasound probe. Template-guided systematic biopsy, template-guided HS targeted, and extended mapping biopsies can thus be performed without auxiliary procedures. The perineal approach may reduce variables affecting needle placement and allow for longitudinal sampling of the prostate that may more accurately biopsy the anterior portion while also limiting infection risk associated with transrectal sampling. [4]

The purpose of this review is to summarize the existing studies evaluating the performance of HS within the prostate cancer paradigm through evaluation of HS in the role of disease detection, disease volume prediction and as a tool for local staging.[19, 20]

Methods Section:

Literature Review-
A search of PubMed up to April 2017 was used to identify eligible studies evaluating the use of HS in prostate cancer evaluation. The search terms utilized were “histoscanning” and “prostate.” All identified studies were then examined by two reviewers. Any original study available in English addressing PCa and HS was considered relevant to the current review and included in the analysis. Additional articles were found through references and also included in the review.

Results:

Literature Review-

The search returned 29 results, of which 11 were original articles published in English. An additional 7 articles found through references were also included.

Detection of Prostate Cancer

Table 1 illustrates the results from studies reporting on the HS cancer detection rate (CDR) compared to radical prostatectomy (RP). The study populations ranged from 13 to 282 patients and evaluated cancer detection rates on patient and sextant basis. The reported sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) ranged from 16 to 100%, 45 to 82%, and 52 to 100% respectively. HS CDR for cancer foci greater than 0.5 mL was reported in 5 studies and reported a NPV ranging from 57 to 100% and PPV ranging from 47 to 80%. Four studies reported HS CDR for cancer foci greater than 0.2 mL with NPV ranging from 52 to 83% and PPV 64 to 82%.

Braeckman *et al* first reported a proof of concept study in 2008 on a series of 29 men with clinically localized prostate cancer who underwent HS followed by RP.[16] Of these men, 15 HS studies were used to develop the algorithm for HS detection. This algorithm was then applied to 14 men. This study concluded that index tumor diameter determined by HS correlated with pathology index tumor diameter (r=0.95, p <0.001). This study further reported a 100% concordance between HS and RP pathology regarding multifocal vs. unifocal and unilateral vs. bilateral disease. Additionally, the authors reported that HS accurately predicted extracapsular extension in 3 of 4 RP specimens. Braeckman *et al* followed this proof of concept study with a further analysis of the same 13 "test" subjects (one of the initial 14 patients was removed from analysis due to damage to the RP specimen).[21] The purpose of the second analysis was to report on HS CDR for cancerous lesions ≥ 0.5 mL as well as a comparison of the total cancer volume (TCV) on HS to RP tumor volume. Of these 13 men, RP histology demonstrated 12 total tumors that with a volume ≥ 0.5 mL. Histoscanning™ correctly identified each of these tumors, providing a sensitivity of 12/12 (100%). Histoscanning™ did not detect 3 of 16 tumors smaller than 0.5 mL, resulting in a specificity of 13/16 (81%). The authors reported a PPV and a NPV of 80% and 100% for tumors ≥ 0.5 mL. Furthermore, the authors reported a strong correlation between HS tumor volume and RP histologic tumor volume (HTV) (r = 0.99, p < 0.001).

Seeking to reproduce these promising initial results, Simmons *et al* reported the results of a prospective, multi-institutional study on 27 men with clinically localized prostate cancer who underwent HS prior to RP.[22] On lesion analysis, the authors reported that HS detected 21 of 23 tumors with volume ≥ 0.5 mL (sensitivity 91%) when using the manual volume method and 19 of 23 (83% sensitivity) when using the HS embedded software. Further evaluation of CDR for HS on a sextant basis for the 23 tumors with a volume ≥ 0.5 mL demonstrated a sensitivity, specificity, PPV and NPV of 90%, 70%, 80% and 84% respectively. For tumors ≥ 0.2 mL, HS detected 25 of 27 cancer foci using both the manual volume and embedded methods

(sensitivity 91%). Evaluation of all tumors (27 men, all tumors identified were greater than 0.2 mL) demonstrated a sensitivity, specificity, PPV and NPV of 90%, 72%, 82% and 83% respectively. The total cancer volume determined by manual estimation on HS correlated with histologic total cancer volume with a correlation coefficient of r =0.72, while the HS total cancer volume using the embedded software volume tool correlated with histologic total cancer volume with a correlation coefficient of r = 0.41. The decrease in correlation accuracy between HS determined volume and HTV was evaluated with a multivariate linear regression analysis and the authors state that the distance from the TRUS probe to the posterior prostate capsule significantly impacts the accuracy of the US volume measurement. They report that a distance of less than 3.5 mm between the TRUS probe and the posterior capsule result in more accurate volume measurements and that 9 of the 27 (33%) patients in the study had distances greater than 3.4 mm.

Javed *et al* performed a prospective analysis in a similar fashion aimed to verify the results of Simmons and Braeckman.[23, 24] This study evaluated 24 patients undergoing HS prior to RP. Using only manual tumor evaluation, they reported no correlation between HS tumor volume and HTV, even when correcting for tumor shrinkage. This study demonstrated a significantly lower diagnostic accuracy for HS than prior evaluations, reporting a sensitivity, specificity, PPV, and NPV of 37%, 71%, 41% and 67% for lesions ≥ 0.5 mL and 63%, 53%, 64%, and 52% for lesions ≥ 0.2 mL, respectively. They further evaluated the ability of HS to detect and locate the index lesion as found on RP and reported a sensitivity, specificity, PPV, and NPV of 61%, 53%, 58% and 56%, respectively. Finally, this study evaluated the ability of HS to detect and locate EPE and found concordance on 11/24 RP specimens. Comparing EPE on RP specimen with HS demonstrated a specificity, sensitivity, PPV, and NPV of 24%, 100%, 35%, and 100%, respectively. These authors noted that the mean US probe distance to the posterior capsule was 2.4 mm.

Macek *et al* prospectively compared HS to RP specimens in 98 men, evaluating detection at a lower threshold of lesions: ≥ 0.1 mL, which is the minimum volume reported by HS software.[25] This study evaluated the prostate divided into 12 sectors and reported HS as positive in 523/1176 sectors (44.5%) while RP histopathology was positive in 473 (40.2%) of these sectors. The reported sensitivity and specificity for detection of prostate cancer was reported as 60% and 66%, respectively. These authors commented on factors influencing accuracy of HS cancer detection and found that overall HS performance was significantly affected by rectal distance, cancer location, index tumor volume, and total cancer volume. The diagnostic accuracy of HS was best in the posterior sectors (sensitivity and specificity of 77% and 39%) compared to 28% and 85% in the anterior sectors.

Porres *et al* reported the largest study of 282 men to date using a similar study design, although they excluded clinical stage T3b or higher, prior TURP, prostate volume > 60 mL and posterior US signal loss (e.g. prostate calculi) > 0.5 mL.[26] Histoscanning™ tumor volume was calculated using embedded software. This study reported poor correlation between HS tumor volume and HTV (Lin's concordance correlation coefficient was calculated as 0.064, poor agreement). The detection and localization of prostate cancer foci by HS was evaluated on a sextant basis and

stratified according to detection threshold of > 0.2 mL and > 0.5 mL. The sensitivity and specificity for either threshold ranged widely and are shown in Table 1. Of note, the authors report that the mean US probe to posterior prostate distance was 4 mm.

Orcyzk *et al* compared HS disease detection in 31 men undergoing RP with preoperative multi-parametric MRI (mpMRI).[27] In 31 men, 84 tumors were identified on RP. Histoscanning™ detected 36 of these, demonstrating CDR of 42.9%. In contrast, mpMRI detected 42/84 (50%). For cancers with Gleason Sum > 6, mpMRI detected 19/22 (86.4%) while HS detected 11/22 (50%) which was significantly lower than mpMRI (p = 0.0078). The overall diagnostic accuracy of HS and breakdown on apex, base, anterior and posterior are detailed in Table 1. Overall, these authors reported that mpMRI diagnostic accuracy outperformed HS while the overall diagnostic accuracy generally agrees with the results published by Javed *et al* and Porres *et al*.

Simmons *et al* seek to study the negative predictive ability of two diagnostic tools, Histoscanning™ and multiparametric-MRI (mpMRI), in ruling out clinically significant prostate cancer (defined as Gleason Sum ≥ 4+3 and maximum cancer core length ≥ 6mm). This prospective study aims to compare these two index tests against transperineal template prostate mapping (TPM) biopsies in men who have previously undergone TRUS biopsy but whose diagnosis remains unclear either due to high PSA or strong clinical suspicion. At the time of HS and mpMRI, the subjects will undergo two targeted biopsies based on regions defined by HS and two more based on mpMRI followed by 5mm sampling through a brachytherapy grid. Additionally, the study plans to examine differences in detection of MRI/US fusion versus cognitive registration. As of March 2017, results from the mpMRI arm of the study have been published but have not been included in this review.[35]

Determination of Tumor Volume

Table 2 lists the results from studies comparing the tumor volume (TV) detected on HS as compared to TV on prostatectomy specimen.

In the initial pilot study, Braeckman *et al* reported that index tumor diameter determined by HS correlated with pathology index tumor diameter (r=0.95, p <0.001). They then reported a follow up study demonstrating a strong correlation between HS tumor volume and RP histologic tumor volume (HTV) (r = 0.99, p < 0.001), using 13 of the original 14 patients used to validate the “proof of concept” study.[5, 6]

Simmons *et al* reported a HS tumor volume correlation to HTV with a correlation coefficient of r =0.72 on manual estimation, and a correlation coefficient of r = 0.41 for software based volume estimation. The authors attributed this difference to 9/27 patients TRUS measurements being performed with TRUS to prostate capsule distances > 3.4 mm.

Javed *et al* used only manual tumor evaluation and reported no correlation between HS tumor volume and HTV, even when correcting for tumor shrinkage. They reported a correlation coefficient for tumor volume of r = – 0.07 and r = – 0.065. The authors claimed that

representatives of the manufacturer of HS confirmed that they were using the device correctly and that their volume measurements were correct. These authors also reported that the mean US probe distance to posterior capsule was 2.4 mm.

Schiffmann *et al* reported on the HS evaluation of tumor volume for 148 men who underwent HS prior to RP.[28] This study reported that tumor volume as measured on HS underestimated HTV on RP. They reported an overall correlation coefficient of r = -0.0083. To address potential for bias within their study design, they incorporated a blinded re-analysis which agreed with the initial HS tumor volume measurement and reported a correlation coefficient of r = 0.039. They further stratified HS tumor volume measurements by D'Amico risk category, prostate volume, HS user experience level, TRUS to prostate distance ($\leq$ 3.5 mm and > 3.5 mm) and HS quality and reported no correlation.

Porres *et al* reported a mean underestimation of tumor volume on HS compared to HTV of 9%. They noted a statistically significant difference in mean tumor volume with HS mean measured as 2.59 mL and HTV measured as 5.30 mL. ($p < 0.0001$). They noted that the discrepancy between HS tumor volume and HTV increases as tumor volume increases. The authors report that the mean US probe to posterior prostate distance was 4 mm.

Histoscanning ™ To Predict Adverse Pathology on Radical Prostatectomy

Compelled by initial studies reporting an NPV of 100% for tumors $\geq$ 0.5mL and the possibility of using HS to predict the presence of EPE, several studies reported on the predictive accuracy of HS for predicting adverse outcomes on RP. These studies are detailed in Table 3.

Salomon *et al* evaluated HS prior RP in 80 consecutive men undergoing RP with intrafascial nerve sparing with intraoperative frozen section.[29, 30] Frozen section was positive for cancer in 38 of 160 (24%) and EPE was diagnosed on final pathology in 12/80 (15%). The HS results demonstrated either no focus of cancer or a focus of cancer < 0.2 mL in 65 (81%). The diagnostic accuracy of HS to predict successful ipsilateral nerve-sparing was reported as sensitivity, specificity, PPV and NPV of 48%, 84%, 34% and 91%, respectively. Frozen section was positive in 6 of 65 regions deemed negative on HS, providing a false negative rate of 9.2%. Univariable and multivariable logistic regression demonstrated that side-specific HS cancer foci volume > 0.2 mL were associated with positive frozen section on the affected side and a 3.7 fold increased risk of nerve resection on the affected side.

As detailed above, Javed *et al* reported a binomial analysis of the location of EPE by prostate sextant on HS compared to RP specimen.[23] They reported a sensitivity and specificity of 78% and 68%, respectively for identifying EPE by sextant. On whole gland analysis for EPE anywhere within the gland, they reported a HS sensitivity and specificity of 100% and 24%, respectively.

Schiffmann *et al* collected HS data on 131 men presenting for RP and evaluated the HS signal at each seminal vesicle and compared these to RP specimen in order to assess for diagnostic accuracy for seminal vesicle invasion (SVI).[31] Pathologic evidence of SVI was found in 23/131

(17.5%) and HS predicted SVI in 123/131 (93.9%). On SV analysis, HS predicted SVI in 229/262 (87.4%). The diagnostic accuracy for SVI stratified by increasing disease threshold levels is detailed in Table 3. Further subset analysis was conducted of men considered high risk by D'Amico criteria (34 men, 68 SV's). On this analysis, HS demonstrated improved PPV, as detailed in Table 3. The area under the curve (AUC) for HS prediction of SVI was 0.54 and 0.56 within the D'Amico high risk subset. For comparison, the authors reported an AUC for SVI on the Partin tables for this cohort of 0.81.

In an abstract presentation, Simmons *et al* presented data on the ability of HS to discriminate between Gleason Pattern 3 and dominant Gleason Pattern 4 or greater in a series of 3 men. This small study reported that 6 of 14 (42.9%) 5 x 5 mm regions evaluated contained Gleason Pattern >3. The relative risk of grids being labeled as predominantly > Gleason Pattern 3 on HS was 3.2 (95% CI 3.0-3.3, $p < 0.0001$). [37]

How Accurate is Histoscanning ™ in Detecting Prostate Cancer at Prostate Biopsy?

Table 4 summarizes studies reporting results of HS at the time of prostate biopsy.

Nunez-Mora *et al* prospectively performed HS prior to prostate biopsy on 32 men (8 biopsy naïve, 14 with prior negative prostate biopsies, 8 on active surveillance and 2 with pT1a carcinoma).[32] They performed HS, analyzed results, and biopsied suspicious regions with 2 cores and employed both transrectal and transperineal biopsy depending upon the location of region of suspicion determined by HS. Each procedure was performed under general anesthesia. They report using a sextant approach with 2 biopsy cores for each transrectal biopsy. For regions that were not accessible by a transrectal biopsy approach, 2 biopsy cores using a transperineal approach were employed. The authors do not provide a breakdown of biopsy cores. Histoscanning™ identified 103 suspicious sites and 72 regions were found to contain cancer on biopsy. Analysis included prostatic intraepithelial neoplasia (PIN) along with cancer diagnosis as positive results when evaluating HS performance. Cancer was detected in 25 of 32 men (CDR 78.1%). The study reported a sensitivity, specificity, PPV, and NPV for HS at biopsy of 93.5%, 79.5%, 67.3% and 96.5%, respectively. They reported false positive regions in 20 of 32 patients (62.5%), for a total of 35 (45.6%) false positive suspicious regions. False negative regions were detected in 5 (16%) patients, with only one (20%) of these regions containing > Gleason Sum 6 and 2 (40%) containing PIN. No further detailed analysis was provided regarding location of positive biopsy or rates of cancer detection in each patient subset (i.e. biopsy naïve vs. active surveillance).

Javed *et al* reported on a biopsy series using HS prior to transrectal biopsy and a series using HS prior to transperineal template biopsy (TTB).[24]

In the transrectal biopsy study, 24 consecutive men underwent HS prior to TRUS biopsy. Suspicious regions identified on HS were biopsied separately from standard sextant biopsy and CDR for targeted biopsy to HS suspicious regions was compared to CDR for whole gland TRUS biopsy. The laterality of HS guided biopsy cancer detection was compared to laterality

determined by TRUS biopsy and HS targeted biopsy cancer detection was compared to TRUS biopsy CDR on a sextant basis. Histoscanning™ detected suspicious regions in 21 of 24 men (88%). The details of each analysis are shown in Table 4. Eight of 21 targeted biopsies contained cancer, for a targeted biopsy CDR of 38.1%.

The TTB study evaluated 57 consecutive men undergoing biopsy as part of initial diagnostic work up or as part of an active surveillance protocol utilizing a TTB. Sixteen (28%) of the study population were on active surveillance. Fifty-six (98%) of the population had a prior negative biopsy (12% had a prior TTB) and 1 man (2%) was biopsy naïve. Two operators performed the biopsy. One operator was blinded to the results of the HS prior to TTB and performed the standard TTB. A second operator evaluated HS results and biopsied any suspicious regions using up to 6 additional targeted biopsy cores. Cancer detection from HS suspicious regions was compared to cancer detection on whole gland in TTB. The laterality of HS targeted biopsy was compared to laterality detected on TTB and HS targeted biopsy CDR was compared to CDR on TTB in sextants. Cancer was detected in 31 of 57 men (54.1%). Suspicious regions were detected on HS in 52 (91%) of study patients. Of these, cancer was detected in 31 of 52 regions (PPV 60%). Detailed analysis of TTB biopsy results are shown in Table 4. Overall CDR for HS targeted TTB was 13.4% of patients with findings and 14% on a lesion basis. No data regarding grade of cancer diagnosis on HS targeted biopsy was provided.

De Coninck *et al* reported results of HS in a consecutive series of 94 men being evaluated for prostate cancer screening (PSA > 4 ng/mL, abnormal DRE, or family history of PCa).[15] Of these 94 men, 37 (39%) were found to have no suspicious regions on initial HS. Fifty-seven (61%) of the initial 94 men were found to have suspicious regions on HS: 24 (26%) had HS tumor volume < 0.5 mL and 33 (35%) had HS tumor volume $\geq$ 0.5 mL. Ultimately, 41 men (43.6%) underwent prostate biopsy. Prostate biopsy was performed using a transrectal approach with the number of biopsies varying by prostate gland. Regions found to be suspicious on HS were biopsied twice. Of the 41 men undergoing prostate biopsy, 17 (41%) were diagnosed with prostate cancer. Fifty-two HS targeted biopsy cores were taken, of which 30 (58%) were positive. Random biopsy cores were positive in 13%. No difference in detection of aggressive prostate cancer was detected between HS targeted cores and random biopsy cores.

Hamann *et al* evaluated the CDR for transrectal and transperineal HS targeted biopsy in 80 consecutive men.[33] Histoscanning™ was performed at a separate event prior to biopsy. Biopsy was performed under anesthesia and 3 targeted cores were taken transrectally for each suspicious region, up to a maximum of 3 locations. The suspicious regions were then biopsied transperineally with 3 biopsy cores per target. Of the 80 men, 30 (37.5%) had undergone a prior prostate biopsy and HS detected lesion in 38 (47.5%) of men. The cancer detection rate on systematic biopsy, transrectal HS targeted biopsy and transperineal HS targeted biopsy was 27.5% 18.75% and 28.75%, respectively.

Schiffmann *et al* retrospectively analyzed cancer detection on prostate biopsy for 198 men with HS prior to biopsy.[34] Cancer detection rates for HS targeted biopsies to corresponding sextants were analyzed using HS volume thresholds of > 0 mL, > 0.2 mL and > 0.5 mL. The

reported sensitivity, specificity, PPV and NPV for > 0 mL, > 0.2 mL and > 0.5 mL were 84.1%, 27.7%, 29.5% and 82.9%; 60.9%, 50.6%, 28.8% and 79.7%; 40.1%, 73.3%, 33.1% and 78.8%, respectively (see Table 4). A subgroup analysis of 141 men undergoing HS at the time of biopsy demonstrated sensitivity, specificity, PPV and NPV for > 0 mL, > 0.2 mL and > 0.5 mL were 76.1%, 32.7%, 19.6% and 86.4%; 48.0%, 51.7%, 17.6% and 82.2%; 32.0%, 76.7%, 22.7% and 84.0%, respectively. A further subgroup analysis by the authors demonstrated that HS volume did not predict higher Gleason Sum score on biopsy. The authors report a false-positive rate for HS of 73.1% and an AUC of 0.58 for HS predicting cancer on biopsy.

Hamann *et al* further evaluated HS prior to repeat prostate biopsy in 97 consecutive men undergoing repeat biopsy.[35] Biopsies were performed under anesthesia using 3 targeted transperineal HS targeted biopsies per suspicious region (maximum of 3 suspicious regions per patient) followed three targeted cores via a TRUS approach. Each patient was also sampled with a 14 core systematic TRUS biopsy. Table 4 shows diagnostic performance results of transperineal HS targeted biopsy combined with targeted TRUS biopsy. Overall CDR between combined HS targeted biopsy and systematic biopsy were similar on a per patient basis, although HS targeted biopsy was significantly higher than systematic biopsy on a sector basis. They reported 1 Gleason Sum > 6 cancer missed on transperineal HS targeted biopsy and 3 Gleason Sum > 6 cancers missed on transrectal HS targeted biopsy. This study also demonstrated no correlation between Gleason Sum score and tumor volume detected on HS.

Sivaraman *et al* reported on the use of real-time HS targeting using a novel software platform called Histoscanning™-True Targeting (PHS-TT).[36] This software platform provides TRUS biopsy guidance to HS targets in real time. This study evaluated PHS-TT in 43 men using targeted cores (2 targeted cores for target volumes > 0.2 to 0.5 mL and three cores for target volume > 0.5 mL) followed by 12 core systematic biopsy. The overall CDR was 46.5% with CDR for PHS-TT biopsy 26% (11/43) and systematic biopsy 44% (19/43). The authors reported a significant increase in % cancer/core length for positive PHS-TT cores compared to systematic biopsy (55.4 vs. 37.5%, $p < 0.05$).

A follow up study by Schiffmann *et al* further investigated the use of PHS-TT in 40 consecutive men.[37] Targeted biopsy was performed using PHS-TT by a single operator followed by systematic biopsy by a second operator blinded to HS findings. An overall CDR of 50% (20) was reported. Systematic biopsy detected cancer in all 20 men (100%) while PHS-TT detected cancer in 8 men (40%, $p = 0.002$). Systematic biopsy detected 12 cancers that were not detected by PHS-TT. On an octant sampling basis, 64 (20.1%) were found to contain cancer. Octant sampling by PHS-TT was positive in 12 (18.8%) compared to 59 (92.2%) for systematic biopsy. Five octants (7.8%) were positive on PHS-TT while negative on systematic biopsy. Of these, 2 (3%) were Gleason Sum > 6. Systematic biopsy detected Gleason pattern 4 dominant disease in 1 octant (1.5%) that PHS-TT diagnosed as Gleason Sum 3+4. Overall, the study reported the AUC for PHS-TT biopsies at 0.5 and a false-positive rate on HS of 82.6%.

Discussion:

Transrectal ultrasound imaging of the prostate significantly improved evaluation of prostate disease[38], ultimately becoming incorporated into the standard urology toolset. Prostate evaluation with TRUS is cost-effective, readily employed, portable, minimally invasive and universally understood by urologists across practice settings. Despite over nearly 30 years of increasing utilization, TRUS prostate imaging remains limited in its ability to distinguish cancerous prostate tissue from non-cancerous.[39-41]. Most series report cancer detection rates for TRUS guided systematic, random sampling ranging from 23 to 38%. [42-44] Reported sensitivity (18-96%) and specificity (46-91%) range widely.[45, 46] Random, systematic TRUS guided prostate tissue sampling results in a false negative biopsy in approximately 30% of cases, as well as an inaccurate disease grade in more than 30% of cases.[4, 47, 48]

As a result of these well-recognized limitations, as well as an increased awareness of the overdiagnosis of low grade, indolent prostate cancer driven by random tissue sampling, multiple investigations into enhancements in TRUS imaging, multi-parametric MRI and elastography have increased.[11]

Histoscanning™ has been evaluated as a possible method for improving TRUS based prostate cancer evaluation since 2008. The initial studies by Braeckman *et al* reported impressive disease detection results including a 100% sensitivity for disease $\geq$ 0.5 mL, NPV of 100%, excellent correlation between HS derived tumor volume and HTV on RP specimens (r=0.99) and a high rate of accurate prediction of EPE (75%).[16]

These initial results appeared to be reproducible after Simmons *et al* reported HS results on 27 men from multiple institutions. While this study did not achieve the same level of sensitivity and specificity as the pilot studies, sensitivity for disease $\geq$ 0.5 mL remained encouraging at 91% and HS measured tumor volume correlated with HTV, r = 0.72.[22] While these results remained promising, the study cohort was again small and highly selected and included data obtained from the initial center responsible for HS algorithm development. This study did acknowledge that US probe to prostate capsule distance appeared to play a role in HS imaging acquisition and interpretation, providing a potential cause for the reported decrease in disease detection accuracy.

As study size has increased, reproducing the initial results has proven difficult. Schiffmann *et al* found no correlation between HS measured TV and RP HTV in 148 men with HS prior to RP.[28] Porres *et al* reported on the largest evaluation of HS prior to RP in 282 men and found that HS tumor volume did not match RP HTV nor did HS accurately determine disease localization on a sextant basis (AUCs varied from 0.54 to 0.71).[26] These authors concluded that HS did not significantly improve prostate cancer diagnostic evaluation. Additional studies on RP specimens demonstrated poor diagnostic accuracy for predicting advanced disease stage (EPE or SVI).

A similar story has also been observed with application of HS to prostate biopsy. Initial studies on a small sample size reported PPV of 68% and NPV of 97% for HS targeted biopsy.[32] As sample size has increased, diagnostic accuracy has again become elusive. Schiffmann *et al* reported an AUC of 0.58 for HS prior to prostate biopsy in the largest published series of HS prior to biopsy.[34] Incorporating HS into real-time biopsy workflow, PHS-TT failed to improve disease detection, demonstrating an AUC of 0.5 and a high false-positive rate of 82.6%.[37]

Overall, these studies demonstrate that HS does not appear to improve diagnostic accuracy for prostate cancer detection, disease localization or risk stratification. While several factors have been highlighted as potential errors (e.g. probe-to-capsule distance, bladder volume, ultrasound scan quality and artifacts), most series report controlling for these factors and thus fail to explain the reported poor diagnostic accuracy. As a calibrated image processing tool, HS may suffer from the same pitfall noted with Computer Assisted Diagnosis platforms applied to mpMRI that demonstrated excellent internal consistency and performances but have failed to overcome the gap to external validation.[49]

The present review also illustrates the tremendous variability in methodologies used to assess performance of an imaging test for detecting and defining prostate cancer. Among the presented studies, variations in the population studied, technique of evaluation (biopsy vs RP), and definition of significant prostate cancer create significant challenges in drawing meaningful comparisons among the results.

Finally, given that mpMRI outperforms HS for disease evaluation, the role of HS in disease detection and biopsy guidance remains dubious.[9, 27, 50]

Conclusion:

Current evidence does not support a significant role for Histoscanning™ in the prostate cancer diagnostic pathway. As image guided prostate biopsy and treatment options continue to evolve, future investigations may identify a role for HS within this framework.

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