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ORIGINAL ARTICLE

True targeting-derived prostate biopsy: HistoScanning™ remained inadequate despite advanced technical efforts

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Abstract
Purpose To verify the reliability of HistoScanning™-based, true targeting (TT)-derived prostate biopsy.
Methods We relied on 40 patients suspicious for prostate cancer who underwent standard and TT-derived prostate biopsy. Sensitivity, specificity, positive predictive value, negative predictive value and the area under the curve (AUC) were assessed for the prediction of biopsy results per octant by HistoScanning™, using different HistoScanning™ signal volume cutoffs (>0, >0.2 and >0.5 ml).
Results Overall, 319 octants were analyzed. Of those, 64 (20.1 %) harbored prostate cancer. According to different HistoScanning™ signal volume cutoffs (>0, >0.2 and >0.5 ml), the AUCs for predicting biopsy results were: 0.51, 0.51 and 0.53, respectively. Similarly, the sensitivity, specificity, positive predictive and negative predictive values were: 20.7, 78.2, 17.4 and 81.6 %; 20.7, 82.0, 20.3 and 82.3 %; and 12.1, 94.6, 33.3 and 82.9 %, respectively.
Conclusions Prediction of biopsy results based on HistoScanning™ signals and TT-derived biopsies was unreliable. Moreover, the AUC of TT-derived biopsies was low and did not improve when additional signal volume cutoffs were applied (>0.2 and >0.5 ml). We cannot recommend a variation of well-established biopsy standards or reduction in biopsy cores based on HistoScanning™ signals.

Keywords HistoScanning™ · Imaging · Prostate biopsy · Prostate cancer · True targeting · Ultrasound

Introduction

Controversial data were recorded for the use of HistoScanning™ at prostate biopsy [1]. The first study on that topic recorded high sensitivity (94 %) and specificity (80 %) in a small patient cohort ($n = 32$) [2]. These encouraging results were not confirmed in larger studies. In particular, low specificity (19–28 %) [3, 4] and area under the curve (AUC) (0.58) were published [3]. Since these previous studies were limited by the inability of HistoScanning™ to perform real-time targeted biopsies [2–4], true targeting (TT) might overcome this burden. This most recent technique combines HistoScanning™ and conventional ultrasound [5].

First results of TT-derived biopsies are now available [5]. Sivaraman et al. [5] investigated 43 patients and proved the feasibility of TT-guided prostate biopsy. Here, the detection rate of TT-derived biopsies was 26 %, and TT-derived biopsy cores achieved higher percentage of cancer involvement than standard biopsy-derived cores (55.4 vs. 37.5 %, $p < 0.05$) [5]. Despite these encouraging findings, 204 TT-derived biopsy cores were performed, but only one additional prostate cancer (PCa) was detected [5]. Additionally,

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no figures were presented according to sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and AUC, respectively. Consequently, there is a need for more evidence to draw valid conclusions regarding the value of TT-derived biopsies.

Based on these considerations, we decided to investigate the reliability of TT-guided biopsies for the detection of PCa. We hypothesize that TT provides reliable prediction of prostate biopsy results.

Methods

Study population

We relied on consecutive patients who underwent prostate biopsy at the Martini-Clinic Prostate Cancer Center between January 2013 and April 2013, performed by a single examiner. All patients were suspicious for PCa based on elevated prostate-specific antigen (PSA), and/or suspicious transrectal ultrasound, and/or suspicious digital rectal examination. Overall, 40 patients and 320 octants were identified. One octant was removed from analyses, based on unknown biopsy results ($n = 319$).

HistoScanning™ and true targeting performance

HistoScanning™ was performed by a single examiner trained in performing TT by Advanced Medical Diagnostics (HistoScanning™ manufacturer). The actual steps in HistoScanning™ are threefold. First, a motorized transrectal ultrasound generates a complete scan of the prostate. Second, the physician defines the region of interest within the HistoScanning™ embedded software. Finally, the computerized HistoScanning™ analyses provide color-coded areas suspicious for PCa, as well as the corresponding tumor volume in non-real-time fashion. The examiner used the biopsy function within the HistoScanning™ embedded TT software and marked the lesions of interest for targeted biopsy. Subsequently, the HistoScanning™ screen splits in two halves showing a still frame of the suspicious lesion on the left side. The examiner is now able to perform a conventional transrectal ultrasound showing the corresponding real-time image on the right side of the screen. With the aim of targeting suspicious lesions from the still frame HistoScanning™ screen, the examiner adjust freehand the transrectal ultrasound until both images (left and right screen) present the same plane of the prostate. Following this cognitive fusion, the examiner is now able to perform a targeted TT-derived biopsy.

Biopsy protocol

First, each patient underwent HistoScanning™ examination followed by TT-guided biopsies. Subsequently, a 10- to 12-core standard prostate biopsy was performed by a second examiner, blinded for previous HistoScanning™ findings. All biopsies were assigned according to eight localizations of the prostate: apex left and right, middle left and right, basis left and right, and median left and right.

Covariates

For each patient, age, prostate volume, PSA, clinical tumor stage and biopsy Gleason score were tabulated.

Statistical analyses

We analyzed the cancer detection rate per patient based on standard and TT-guided biopsies. Additionally, we assumed each octant as a single case and analyzed detection rates for each octant based on standard and TT-guided biopsies, respectively. Sensitivity, specificity, PPV and NPV for the prediction of TT-derived biopsy results were calculated based on octant analyses. In case of positive HistoScanning™ signals, the TT-derived biopsy results were used to verify the prediction of HistoScanning™. In case of negative HistoScanning™ signals, we relied on the standard biopsy results from the corresponding octant of the prostate to verify the prediction of HistoScanning™. Finally, we calculated the AUC for the prediction of TT-guided biopsies. All analyses were performed according to three different HistoScanning™ signal volume cutoffs: >0, >0.2 and >0.5 ml. To account for the non-independency of octants of the prostate, 95 % confidence intervals (CI) were calculated by using a 2000-sample bootstrapping analysis. All tests were two-tailed, and p values <0.05 were considered statistically significant. Statistical analyses were performed with JMP software version 9.0.2 (SAS Institute, Inc., Cary, NC, USA) and RStudio® (version 0.98.945), an integrated development environment for R (version 3.0.1, R Project for Statistical computing, www.r-project.org).

Results

Overall, 40 patients were identified. Baseline descriptives are presented in Table 1. Twenty men (50 %) harbored PCa at prostate biopsy. Of those, the detection was more frequently based on standard than on TT-derived biopsies [$n = 20$ (100 %) vs. 8 (40 %), $p = 0.002$]. Similarly, more patients were exclusively detected by standard than by TT-derived biopsy [$n = 12$ (60 %) vs. 0 (0 %), $p = 0.002$]. The per core detection rate was higher at standard (59/319) compared to TT-derived biopsy cores (12/69) (18.5 vs. 17.4 %, $p = 0.8$). Additionally, no significant differences for the Gleason score were recorded between standard and TT-derived biopsies (Table 2). Finally, the median

Table 1 Baseline characteristics of 40 patients who underwent standard and true targeting-derived biopsy

Parameter	Overall patients, $n = 40$
Age (years)	
Median	65
IQR (range)	58–70 (47–79)
PSA (ng/ml)	
Median	6.3
IQR (range)	5.0–9.8 (0.2–26.0)
Prostate volume (ml)	
Median	44.5
IQR (range)	33.5–60.0 (17.0–109.0)
Biopsy results per patient *n* (%)	
Negative	20 (50)
Positive	20 (50)
Biopsy Gleason n (%)	
3 + 3	10 (50)
3 + 4	3 (15)
4 + 3	2 (10)
≥4 + 4	5 (25)
Clinical tumor stage	
cT1c	18 (90)
cT2a	1 (5)
cT2b	1 (5)
Octant analyses at pathology *n* (%)	
Total octants	319
Negative	260 (81.5)
Positive	59 (18.5)
Octant analyses according to HS signal volume cutoffs *n* (%)	
0 ml	250 (78.4)
>0 ml	69 (21.6)
>0.2 ml	59 (18.5)
>0.5 ml	21 (6.6)

IQR interquartile range, *PSA* prostate-specific antigen, *HS* HistoScanning™

percentage of cancer involvement per positive core was higher at standard than at TT-derived biopsy (21.5 vs. 7.1 %, $p = 0.002$).

Octant analyses

Overall, 319 octants were identified. Sixty-four (20.1 %) octants harbored positive biopsy results. Of those 64 positive octants, the detection was more frequently based on standard than on TT-derived biopsy results [$n = 59$ (92.2 %) vs. 12 (18.8 %), $p < 0.001$]. Similarly, more octants were exclusively detected by standard than by TT-derived biopsy [$n = 52$ (81.3 %) vs. 5 (7.8 %), $p < 0.001$]. Those five octants which were exclusively detected by HistoScanning™ harbored: Gleason 3 + 3 ($n = 3$) and Gleason 3 + 4 ($n = 2$). Overlapping results, representing PCa in both standard and TT-derived biopsies, were recorded in seven octants: Gleason 3 + 3 ($n = 1$), 3 + 4 ($n = 1$), 4 + 3 ($n = 2$) and ≥4 + 4 ($n = 2$). Additionally, in one octant standard biopsy detected Gleason 4 + 3, whereas TT detected Gleason 3 + 4. The HistoScanning™ signal volume was not significantly different between octants with positive versus those with negative biopsy results (mean 0.16 vs. 0.09 ml, $p = 0.1$).

Octant analyses according to HistoScanning™ signal volume cutoff >0 ml

According to HistoScanning™ signal volume cutoff >0 ml, the AUC for predicting positive octants by HistoScanning™ was 0.51 (95 % CI 0.5–0.56) (Fig. 1a). Sensitivity, specificity, PPV and NPV were: 20.7 (95 % CI 10.7–31.3), 78.2 (95 % CI 72.9–83.0), 17.4 (95 % CI 9.0–26.5) and 81.6 % (95 % CI 76.5–86.2), respectively. The corresponding cross tabs are presented in Table 3.

Table 2 Gleason score derived by standard and true targeting prostate biopsies

Parameter	Positive biopsies overall $n = 71$	Standard biopsy $n = 59$ (83.1 %)	TT-derived biopsy $n = 12$ (16.9 %)	*p* value
Gleason score *n* (%)				
3 + 3	30 (42.3)	26 (44.1)	4 (33.3)	0.7
3 + 4	20 (28.2)	16 (27.1)	4 (33.3)	
4 + 3	15 (21.1)	13 (22.0)	2 (16.7)	
≥4 + 4	6 (8.4)	4 (6.8)	2 (16.7)	

TT true targeting

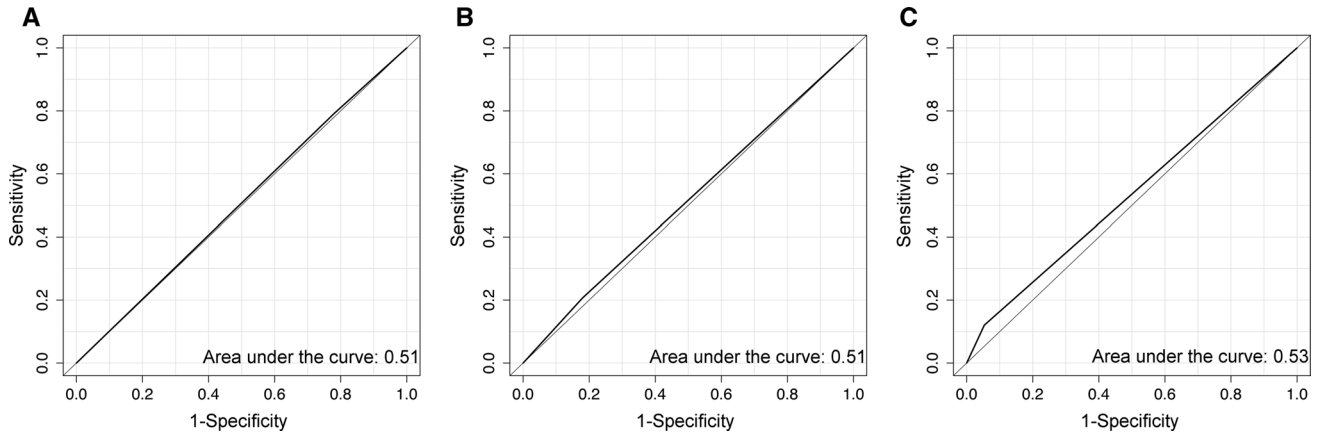

Fig. 1 Area under the curve for true targeting-derived prostate biopsies per octants of the prostate according to different HistoScanning™ signal volume cutoffs: **a** >0 ml, **b** >0.2 ml and **c** >0.5 ml, respectively

Table 3 Cross tabs for predicting biopsy results by HistoScanning™ according to different HistoScanning™ signal volume cutoffs (>0, >0.2 and >0.5 ml) within 319 octants from 40 patients suspicious for prostate cancer

HistoScanning™ signal volume	Positive biopsy	Negative biopsy	*n*
>0 ml *n* (%)	12 (17.4)	57 (82.6)	69
=0 ml *n* (%)	46 (18.4)	204 (81.6)	250
n	58	261	319
>0.2 ml *n* (%)	12 (20.3)	47 (79.7)	59
≤0.2 ml *n* (%)	46 (17.7)	214 (82.3)	260
n	58	261	319
>0.5 ml *n* (%)	7 (33.3)	14 (66.7)	21
≤0.5 ml *n* (%)	51 (17.1)	247 (82.9)	298
n	58	261	319

Octant analyses according to HistoScanning™ signal volume cutoff >0.2 ml

According to HistoScanning™ signal volume cutoff >0.2 ml, the AUC for predicting positive octants was 0.51 (95 % CI 0.5–0.58) (Fig. 1b). The sensitivity, specificity, PPV and NPV were: 20.7 (95 % CI 10.7–31.3), 82.0 (95 % CI 77.2–86.4), 20.3 (95 % CI 10.7–30.5) and 82.3 % (95 % CI 77.3–86.7), respectively. The corresponding cross tabs are presented in Table 3.

Octant analyses according to HistoScanning™ signal volume cutoff >0.5 ml

According to HistoScanning™ signal volume cutoff >0.5 ml, the AUC for predicting positive octants was 0.53 (95 % CI 0.5–0.59) (Fig. 1c). The sensitivity, specificity, PPV and NPV were: 12.1 (95 % CI 3.9–21.1), 94.6 (95 % CI 91.8–97.0), 33.3 (95 % CI 13.3–54.2) and 82.9 % (95 % CI 78.4–86.9), respectively. The corresponding cross tabs are presented in Table 3.

Discussion

We hypothesized that TT provides a reliable prediction of prostate biopsy results. To test our hypothesis, we relied on octant analyses from 40 patients, suspicious for PCa, who underwent standard and TT-derived prostate biopsies. Unfortunately, we were not able to confirm our hypothesis.

The AUC for TT-guided biopsies was only 0.51, which is similar to flip of a coin (AUC 0.5). Similarly, the sensitivity of 20.7 % and specificity of 78.2 % were inadequate for a reliable prediction of biopsy results. These discouraging findings were driven by a high rate of false-positive HistoScanning™ signals (82.6 %). Since little artifacts might have influenced these results, we adjusted the analyses for additional HistoScanning™ signal volume cutoffs >0.2 and >0.5 ml, respectively. Despite these adjustments, the AUC for TT-guided biopsies remained discouraging: 0.51 and 0.53, respectively. Similarly, the sensitivity and specificity remained unreliable: 20.7 and 82.0 %, and 12.1 and 94.6 %, respectively. Since TT results remained unreliable even in the signal volume range >0.5 ml, it is highly doubtful whether HistoScanning™ will be able to truly separate significant from insignificant PCa [6].

Our study adds important information to the existing literature. To the best of our knowledge, TT was analyzed in only one publication so far. Similar to our study, Sivaraman et al. [5] investigated 43 patients who underwent standard and TT-derived prostate biopsies [5]. Despite the fact that standard biopsy cores achieved lower percentage of cancer involvement than TT-derived cores (55.4 vs. 37.5 %, $p < 0.05$), similar to our study, the PCa detection rate was higher at standard than at TT-derived biopsy (44 vs. 26 %).

Similarly, standard biopsy achieved superior detection rates per core compared to TT (17.4 vs. 15.2 %). Moreover, 204 additional TT-guided biopsy cores were performed, but only one cancer was exclusively detected by TT. It is uncertain whether the one additional PCa detection was based on HistoScanning™ findings or a random event. Regardless of the explanation, the gain is marginal at best.

The observed results for TT are somehow frustrating, especially because TT represented a dawn of hope, after several negative reports regarding HistoScanning™ at prostate biopsy [3, 4]. In particular, Javed et al. [4] recorded lower detection rates at HistoScanning™-derived biopsy compared with standard biopsy (13 vs. 54 %). Additionally, sensitivity and specificity of were 100 and 19 %, respectively. In so far the largest study, Schiffmann et al. [3] relied on data from 198 men and compared HistoScanning™ results from 1188 sextants with the corresponding biopsy findings. The AUC for HistoScanning™ to predict positive biopsy results per sextant was only 0.58 (95 % CI 0.55–0.62). Similarly, the sensitivity and specificity were only 84 and 28 %, respectively. These data questioned first promising results from Nunez-Mora et al. [2]. They relied on only 32 patients who underwent HistoScanning™ prior to prostate biopsy. Conversely, to our study, sensitivity, specificity, PPV and NPV were 94, 80, 68 and 97 %, respectively. Besides the small sample size, the study was limited by the inclusion of patients with established PCa (31 %) prior to biopsy [2]. It is of note that the authors identified HistoScanning™ signal suspicious for PCa to be true-positive, even in cases with exclusive prostatic intraepithelial neoplasia. These non-TT-derived biopsy studies [2–4] were limited by the inability of HistoScanning™ to perform real-time targeted biopsies. Consequently, it remains doubtful whether the actual biopsy core was truly derived from the suspicious area identified by HistoScanning™. To unravel this limitation, TT technology was implemented. However, based on the current study it seems that despite advanced technical efforts, HistoScanning™ remained inadequate at prostate biopsy.

Controversial and at times conflicting results were also presented according to other HistoScanning™ studies [1]. In particular, first data were published in 2008 and relied on a very small patient sample ($n = 14$) [7, 8]. Here, most favorable results were recorded, when correlating the maximal tumor diameter between HistoScanning™ and final pathology at radical prostatectomy ($r = 0.95$, $p < 0.001$) [7]. Additionally, the sensitivity and specificity for the detection of cancer foci according to HistoScanning™ signal volumes ≥0.5 ml were 100 and 81 %, respectively [8]. Unfortunately, subsequent analyses reported controversial results. Specifically, the sensitivity and specificity were only 37 and 71 %, when detecting cancer foci according to HistoScanning™ signal volumes ≥0.5 ml [9]. Similarly, the AUC was only 0.63, when using HistoScanning™ for the detection of cancer foci ≥0.1 ml in 98 patients [10].

Similarly, no correlation was recorded between the total tumor volume assessed by HistoScanning™ and final pathology results at radical prostatectomy ($r = -0.008$, $p = 0.9$) [11]. Discouraging results were also detected, when seminal vesicle invasion was predicted by HistoScanning™ prior to radical prostatectomy. Here, Schiffmann et al. [12] relied on 131 patients and 262 seminal vesicles. The sensitivity and specificity of HistoScanning™ for the detection of seminal vesicle invasion were only 77 and 11 %, respectively. Subsequently, the AUC for the prediction of seminal vesicle invasion was only 0.54 [12]. Moreover, even in patients with D'Amico high-risk criteria ($n = 34$), sensitivity and specificity were only 74 and 13 % with an AUC of 0.56, respectively [12].

Despite its strengths, our study has limitations. First, our study results rely on a small group of patients ($n = 40$). Consequently, more evidence is needed to either confirm, or question our results. Second, standard biopsy results were used to verify the prediction of negative HistoScanning™ findings. Final pathology after radical prostatectomy might represent a more reliable verification. However, on the one hand, such data are difficult to obtain, and on the other hand, such analyses could only include patients with diagnosed PCa. Third, artifacts might have caused false-positive results. However, we aimed to control for possible artifacts by analyzing additional HistoScanning™ signal cutoffs (>0.2 and >0.5 ml). Moreover, in terms of practicability it is negligible whether poor results were driven by artifacts or not. Finally, based on the novelty of TT technology, learning curve issues might have biased the current study results.

In conclusion, the prediction of biopsy results based on HistoScanning™ signals and TT-derived biopsies was unreliable. Moreover, the AUC of TT-derived biopsies was low and did not improve when additional signal volume cutoffs were applied (>0.2 and >0.5 ml). We cannot recommend a variation of well-established biopsy standards or a reduction in biopsy cores based on HistoScanning™ signals. However, the investigated study population was small and more evidence is needed to draw final conclusions regarding the value of TT-derived biopsies.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest according to the current manuscript.

Ethical standard The current manuscript has no conflict with ethical standards set by the Declaration of Helsinki.

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