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ORIGINAL ARTICLE

Precision of MRI/ultrasound-fusion biopsy in prostate cancer diagnosis: an ex vivo comparison of alternative biopsy techniques on prostate phantoms

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Abstract

Purpose Comparing the accuracy of MRI/ultrasound-guided target-biopsy by transrectal biopsy (TRB) with elastic versus rigid image fusion versus transperineal biopsy (TPB) with rigid image fusion in a standardized setting.

Methods Target-biopsy of six differently sized and located lesions was performed on customized CIRS 070L prostate phantoms. Lesions were only MRI-visible. After prior MRI for lesion location, one targeted biopsy per lesion was obtained by TRB with elastic image fusion with Artemis™ (Eigen, USA), TRB with rigid image fusion with real-time virtual sonography (Hitachi, Japan) and TPB with rigid image fusion with a brachytherapy approach (Elekta, Sweden), each on a phantom of 50, 100 and 150 ml prostate volume. The needle trajectories were marked by contrast agent and detected in a postinterventional MRI.

Results Overall target detection rate was 79.6% with a slight superiority for the TPB (83.3 vs. 77.8 vs. 77.8%). TRB with elastic image fusion showed the highest overall precision [median distance to lesion center 2.37 mm (0.14–4.18 mm)], independent of prostate volume. Anterior lesions were significantly more precisely hit than transitional and basal lesions ($p = 0.034$; $p = 0.015$) with comparable accuracy for TRB with elastic image fusion and TPB. In general, TRB with rigid image fusion was inferior [median 3.15 mm (0.37–10.62 mm)], particularly in small lesions.

Conclusion All biopsy techniques allow detection of clinically significant tumors with a median error of 2–3 mm. Elastic image fusion appears to be the most precise technique, independent of prostate volume, target size or location.

Keywords Prostate cancer · Accuracy · Target-biopsy · Software-based · MRI/ultrasound image fusion · Comparison

Introduction

MRI/ultrasound-fusion prostate biopsy improves detection of clinically significant prostate cancer compared to conventional systematic biopsy [1–3]. Recent analysis provides evidence for a superiority of a combined targeted and systematic biopsy regime compared to an exclusive targeted biopsy according to cancer detection [4]. Fusion of multiparametric MRI (mpMRI) and ultrasound images can be carried out by cognitive overlaying of the MRI and live ultrasound (visual estimation), by direct MRI/MRI-fusion (in-bore) or by software co-registered MRI/ultrasound-fusion.

Compared to a systematic biopsy, visual estimation shows higher detection rates of significant cancer [5]. However, the technique is operator dependent and requests a considerable learning curve.

Despite its high accuracy, in-bore biopsy is not widespread due to its limited availability, high cost and

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expenditure of time. Further, the reduced number of cores without systematic sampling and up to 10% MRI-invisible significant cancers can lead to a substantial rate of underdetection [6–8].

Therefore, software co-registered MRI/ultrasound-fusion is the most promising technique in target-biopsies at present. The biopsy devices primarily differ in the way of probe tracking and image fusion. Probe tracking can be performed by co-registration within an electromagnetic field or by sensors mounted at the probe. Elastic and rigid image fusion with or without consideration of prostate deformation have to be distinguished [9]. Further, fusion biopsy is feasible via transrectal and via transperineal access and with freehanded or mechanically assisted needle guidance. Many publications demonstrated increasing detection rates of significant cancers in contrast to systematic transrectal or transperineal mapping biopsies [9, 10]. However, only a few studies compared different target-biopsy techniques. In-bore and software co-registered MRI/ultrasound-fusion seem to improve overall cancer detection and detection of clinically significant cancer compared to visual estimation [11, 12]. Another study demonstrated no significant differences between rigid image fusion and visual estimation [5]. Delongchamps et al. [12] constituted that elastic image fusion retrieved more cancer than rigid image fusion.

Commonly, quality of target-biopsies is determined in terms of cancer detection rates compared to systematic biopsy. Previous studies have investigated the precision of newly introduced biopsy systems on prostate phantoms [13–15]. It remains unclear which technique of image fusion and access renders highest accuracy. Patient movement, anatomical differences or mpMRI techniques can further bedevil results. Thus, the intention was to compare the accuracy of three different approaches in a standardized ex vivo setting on prostate phantoms with only MRI-visible lesions.

Materials and methods

Prostate phantoms

Nine customized prostate phantoms (CIRS 070L, CIRS Inc., Norfolk, USA) were used for fusion biopsy. Anatomical structures consist of a tissue equivalent gel. A perineal membrane and rectal wall allows access for both techniques. All phantoms consist of six lesions that are only visible in MRI and are isoechoic in ultrasound. Each lesion of 5 and 10 mm diameter was placed at base, in transitional zone and anterior, respectively (Fig. 1). For each biopsy system, intervention was performed on a phantom of 50, 100 and 150 ml prostate volume.

Pre- and postinterventional MRI

In clinical routine, patients undergo a state-of-the-art multiparametric MRI of the prostate using a clinically established whole-body 3T scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) prior biopsy. High-resolution T2-weighted turbospin echo sequences [repetition time (TR): 3590 ms; echo time (TE): 108 ms; slice thickness: 3 mm] are then utilized for real-time US-fusion in MR-guided biopsies.

Phantoms were imaged using the same scanner and an isotropic 3D T2 space sequence (TR: 1400 ms; TE: 140 ms; slice thickness: 0.7 mm) allowing for 3D reconstructions and precise angulation along biopsy core channels (Fig. 2).
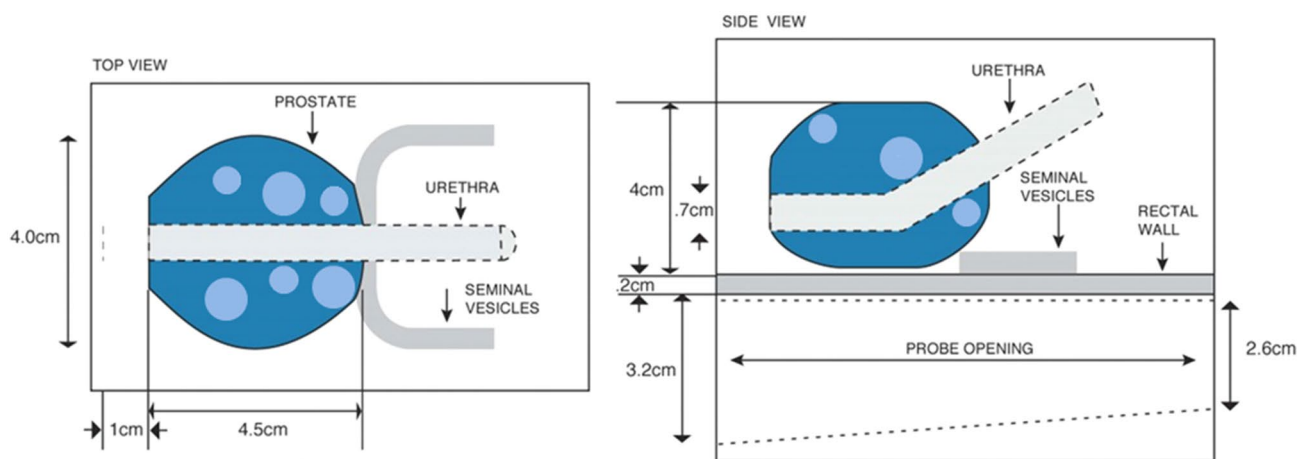
Fig. 1 Schematic illustration of prostate phantoms with the localization of the customized placed MRI-visible lesions. Each of the nine phantoms contains three lesions of a 5 mm diameter and three lesions of a 10 mm diameter arranged identically
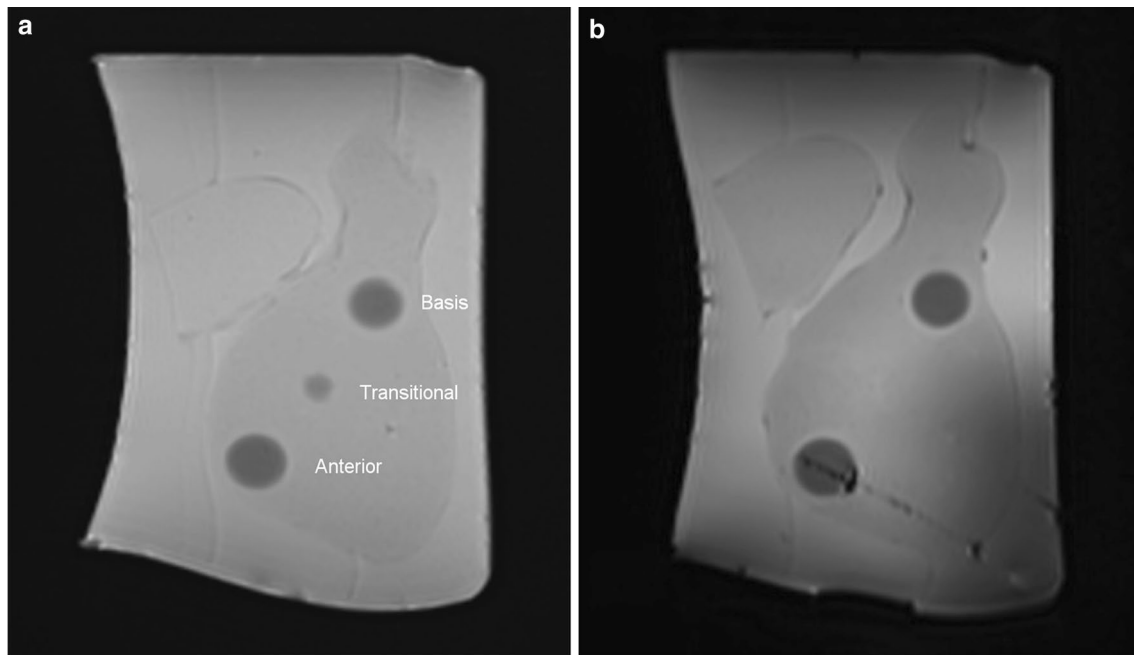
Fig. 2 MRI of a prostate phantom in sagittal view: **a** lesions are visible due to their hyperintensity. Cranial the bladder neck and seminal vesicles are constructed as anatomical landmarks and **b** contrast agent marks the needle trajectory of one anterior placed biopsy

Biopsy systems

Transrectal biopsies were carried out with both elastic and rigid MRI/ultrasound-fusion. Artemis™ (Eigen, CA, USA) is a biopsy device that enables 3D-reconstruction of the ultrasound images and elastic fusion with prior delineated contours of the prostate and regions of interest (ROI) in transversal sections of the MRI. The ultrasound probe is attached to a semi-robotic arm that supports needle navigation controlled by real-time sonography. Probe movements are tracked by encoders in the mechanical arm. All biopsy sites are registered and visualized in the 3D model for exact tumor localization and re-biopsies in case of active surveillance [16].

Real-time virtual sonography (Hitachi Medical Systems, Tokyo, Japan) uses sensor-based tracking of the transrectal ultrasound probe in an electromagnetic field. T2-weighted transversal MRI sequences are loaded on the HiVision Preirus US-device. The lesions have to be circled, and the plane image sections are fused afterward with the live ultrasound image in a rigid form without adaption of the prostate borders. Biopsy is performed freehand thereafter [17].

Brachytherapy equipment is used for transperineal biopsy (TPB) (Nucletron®, Elekta, Sweden) where the biplane transrectal probe is placed on a mechanical stepper. After scanning the prostate in transversal and sagittal view, a 3D model is reconstructed and fused rigidly with the MRI images. A grid on the stepper is mounted near the perineal membrane for needle placement. Live ultrasound allows insertion of the needle into prior marked lesions.

Biopsy sampling

First, for each system preinterventional MRI-visible lesions were delineated in the particular software. We performed one target-biopsy per lesion with a 18 G coaxial needle and a core length of 22 mm. Needle pathway was always planned to cross-lesion center in transversal view. The inner sheet of the needle was removed afterward, and an MRI contrast agent (Gadoteric acid 0.5 mmol/ml, Dotarem, Guerbet) was injected through the indwelling outer sheet to fill out the needle cylinder. The urologists who performed biopsies on the phantoms were experienced in the specific procedure.

Geometrical and statistical analysis

The postinterventional MRI sequences were evaluated in OsiriX DICOM viewer (Pixmeo, Bernex, Switzerland). To increase accuracy, the three-dimensional coordinates of the center of the lesions were determined by arithmetic means of the outermost points of the lesions. The three-dimensional coordinates of the start and end of the needle pathway were determined. The first 2 cm of the needle pathway starting from the tip was defined as the biopsy core. A target hit (and thus hit length) was defined by geometrically calculating the intersection of the biopsy core and target lesion using the aforementioned parameters. Wilcoxon rank sum test was used to compare precision of the systems and target localization.

Table 1 Count of biopsies that were inside a lesion by prostate volume and biopsy system in total and percentage

	50 ml		100 ml		150 ml		All phantoms	
	No.	%	No.	%	No.	%	No.	%
Transperineal	5/6	83.3	6/6	100	4/6	66.7	15/18	83.3
Artemis	6/6	100	3/6	50	5/6	83.3	14/18	77.8
Hitachi RVS	5/6	83.3	4/6	66.7	5/6	83.3	14/18	77.8
All systems	16/18	88.9	13/18	72.2	14/18	77.8		

Results

Overall precision

Among all 54 biopsy cores, 43 hit a lesion (79.6%). Overall TPB revealed one more hit than Artemis and Hitachi RVS (Table 1).

The median precision of a system to guide the needle into a lesion center was 2.37 mm (0.14–4.18 mm) for Artemis, 2.54 mm (0.22–6.88 mm) for TPB and 3.15 mm (0.37–10.62 mm) for Hitachi RVS for all lesions, irrespective of target localization, size and prostate volume (Fig. 3a). No statistical significance could be found.

Target localization

In general, the anterior located lesions were significantly hit more precisely than transitional zone and basal lesions (anterior vs. transitional: $p = 0.034$; anterior vs. basal: $p = 0.015$) (Fig. 3b). Only one of 18 anterior biopsies missed the target (Table 2). TPB and Artemis showed almost the same accuracy in anterior lesions, whereas Hitachi RVS was inferior to both systems. Further Hitachi RVS had higher variance and more spikes in transitional and basal lesions (Fig. 3c).

Target size

Except the anterior 5 mm lesion, detection rates for the 10 mm lesions outbalanced the smaller ones over all systems. TPB and Hitachi RVS biopsies missed more small lesions than Artemis (33.3 and 44.4 vs. 11.1%). Target-biopsies most frequently missed the 5 mm basal lesions (Table 1).

Prostate volume

Target-biopsies achieved highest detection rates (88.9%) for all biopsy systems in the 50-ml prostate phantom. In this small prostate volume, only Artemis accurately targeted the lesions in all six biopsies. TPB and Hitachi RVS were less precise (TPB in 150 ml, Hitachi RVS in 100 ml) with increasing prostate volumes, whereas Artemis yielded a constant distance irrespective of the prostate volume (Fig. 3d).

Discussion

Prostate imaging prior to biopsy became an emerging tool for cancer screening during the past years. Thereby mpMRI accurately detects prostate cancer and index lesions, which has been proven in prostatectomy specimens [7]. Target-biopsy leads to increased detection rates of clinically significant cancer beside a reduced overdetection of insignificant low-risk cancers. Recent data provide correlation for the detection of prostate cancer in general and clinically significant cancer in particular with the PI-RADS score that has been introduced and recently updated for standardization of mpMRI interpretation [18]. Further, mpMRI enables accurate risk stratification in patients with low-risk cancer undergoing active surveillance. However, there are still up to 10% clinically significant cancers missed by mpMRI in combination with a target-biopsy only [8]. Thus, a combination of target and systematic biopsy is recommended. Due to this MRI-interpretation error the intention of this study was to evaluate and compare the precision of target-biopsy systems head-to-head and independent of radiologic inaccuracy.

We analyzed the ability of a biopsy system to detect the center of a target. Biopsy with Artemis™ revealed high precision and the shortest median errors. Two main characteristics of this biopsy platform might explain these advantages. First, the software-based co-registration and elastic fusion of mpMRI and live ultrasound images take into account the differing prostate contours. These occur due to TRUS insertion and deformation of the prostate. Additionally, TRUS probe leads to substantial prostate displacement. Elastic fusion and motion compensation mode allows for continuous adjustment of the fusion, even during biopsy. In contrast, rigid image fusion, as with Hitachi RVS, has a higher mismatch potential. A shift of the fused slices during the TRUS scanning is not mentioned by patient movements or prostate deformations [9].

In addition, the Artemis™ platform supports biopsy navigation with the TRUS probe mounted on a semi-robotic mechanical arm. The arm has four degrees of freedom around the fixed tip of the probe. This leads to reduced probe movement during the scanning and navigation phase to a minimum. By 360° rotation of the probe around
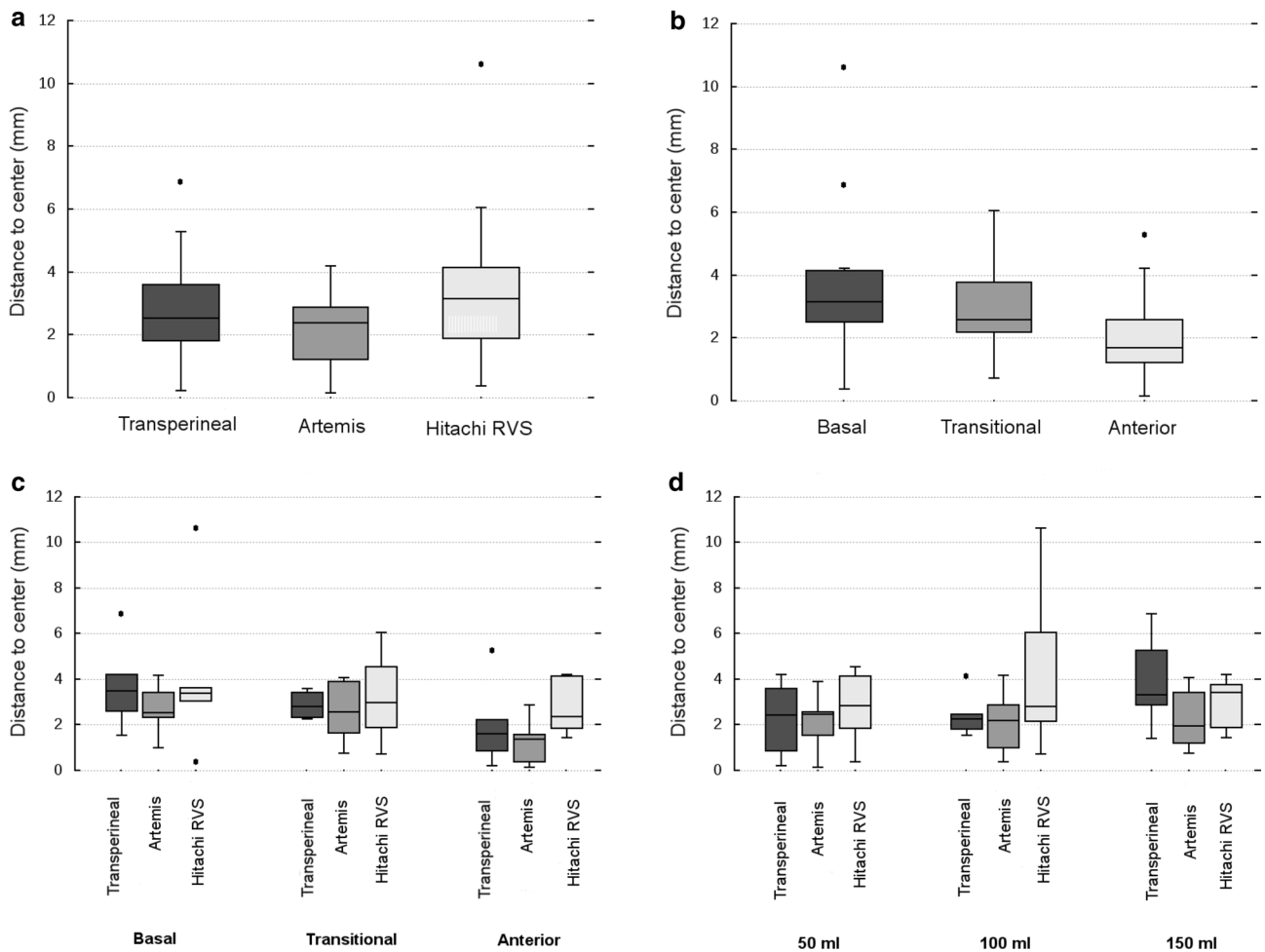
Fig. 3 Demonstration of distances to the lesions center and biopsy deviation, **a** representation of all biopsies per system, **b** overall biopsy precision per target location irrespective of the system, **c** biopsy precision per system and target location and **d** biopsy precision per system and prostate volume

Table 2 Count of biopsies that were inside a lesion by the single lesions in total and percentage

	Basis				Transitional				Anterior			
	5 mm		10 mm		5 mm		10 mm		5 mm		10 mm	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Transperineal	1/3	33.3	3/3	100	2/3	66.7	3/3	100	3/3	100	3/3	100
Artemis	2/3	66.7	2/3	66.7	3/3	100	2/3	66.7	3/3	100	2/3	66.7
Hitachi RVS	1/3	33.3	3/3	100	1/3	33.3	3/3	100	3/3	100	3/3	100
All	4/9	44.4	8/9	88.9	6/9	66.7	8/9	88.9	9/9	100	8/9	88.9

its fixed longitudinal axis, scanning of the prostate in 2D slices renders dataset for 3D-reconstruction. This allows exact biopsy planning and has been investigated formerly by Han et al. [19]. They demonstrated suboptimal freehand biopsy sampling, while robotic assistance optimized accuracy (error 9.0 vs. 1.0 mm) [20].

In our study, TPB hits one more target than TRB with both fusion techniques but showed minimally inferior biopsy precision compared to TRB with Artemis™. Median error was 2.54 mm (0.22–6.88 mm). In basal lesions and high volume prostate of 150 ml TPB demonstrated higher variation and less accuracy. Several other clinical studies

compared cancer detection of TRB and TPB with contro-versial results. Guo et al. [21] found a cancer detection rate of 35.3% for 8–12 core TPB vs. 31.9% for 12 core TRB in a prospective randomized trial. In the series of Scott et al. [22], there was no significant difference between conventional TRUS-guided biopsy and transperineal map-ping biopsy in terms of upgrading in whole mount pathol-ogy (33.22 vs. 30.41%). The analysis of 1.132 prostatec-tomy specimens by Hossack et al. [23] showed that TPB and TRB are similar in tumor size, stage and significance identification.

Biopsy precision was significantly influenced by the location of the lesions. As previously published, a reduced ability of TRB in detection of anterior tumors is based on the apparent difficult biopsy angle. Thus, several studies proposed a separate additional anterior biopsy sampling to avoid underdetection [24, 25]. Whether TPB is superior to TRB in anterior lesions is still being discussed. However, MRI/US-target-biopsy of anterior lesions has been shown to significantly detect more cancer than systematic biopsy [26]. Here, we demonstrate that anterior lesions can be accurately detected by MRI/US-target-biopsy without a dif-ference between TPB and TRB with elastic image fusion.

Except for TRB with elastic image fusion the accuracy and target detection rate decreased with enlarged prostate volumes. It could be hypothesized that in large prostates with TPB the needle has to be guided through more tissue, especially for basal lesions which harbors a higher risk of deviance. In patients with large prostates, the symphysis often barricades transperineal access to anterior. In a pro-spective comparison study, target-biopsy and systematic biopsy had decreasing cancer detection rates for prostate volumes from >30 to 160 ml. However, in more than 40 ml volumes target-biopsy found significantly more cancer than systematic biopsy [27].

TRB with elastic image fusion and robotic assistance hits small targets of 5 mm diameter most accurately. This comes along with previous results of Wysock et al. [11] in their comparison of visual estimation and TRB with elastic image fusion.

To our best knowledge there exists only one study that compares different co-registration systems. Delongchamps et al. [12] based their results in favor of elastic image fusion on population and MRI differences and overall cancer detection rates. It is likely that our findings confirm their suggestion of a higher mismatch when fusing MRI and ultrasound images with rigid nondeformable registration.

This study has some shortcomings. First, the analysis of the biopsy trajectory in the post-biopsy MRI sequence depends on the visual analysis that might harbor some inaccuracies. Further in some biopsy cores the contrast agent diffused around the exact pathway. To rule out these

individual deviations, we analyzed the trajectory in three different views in the three-dimensional MRI sequence within a coordinate plane. Secondly, there were some outli-ers for each biopsy system not conforming to the normal interquartile range. This demonstrates that minor biopsy inaccuracies can lead to substantial deviances among all biopsy systems despite their well-established clinical use. Consequently, the urologist has to focus on an unmitigated exact image fusion and biopsy sampling. Thirdly, this phantom-based study differs from real patient biopsy in two relevant aspects: Whereas the phantom is completely "immobile", patient movement during biopsy in local anes-thesia as well as prostate movement due to breathing can reduce accuracy. Although the phantoms consist of tissue equivalent material and realistic anatomical structures, accuracy of TPB in large prostate volumes is often reduced because of anatomical difficulties caused by the symphysis which is not included in the phantoms. Hence, this harbors the potential risk of a worse target detection and precision for TPB in large prostates than demonstrated in this study.

Summarizing, this evaluation of biopsy precision in an ex vivo setting generated four key findings: (1) elastic image fusion combined with transrectal access permits the highest accuracy to detect an MRI-suspect target, neither affected by prostate volume nor by target size. (2) Anterior localized targets are detected significantly more precisely than transitional zone and basal targets. TRB with elastic image fusion and TPB do not differ in anterior precision crucially. (3) TRB with rigid image fusion in a freehand fashion shows inferiority in overall precision, in anterior precision as well as small target detection. It seems to be prone to deviation. (4) Median distance to a lesion's center is small enough to allow detection of clinically significant tumors according to the definition of a cancer volume of more than 0.5 ml with all target-biopsy systems [28].

Conclusion

This ex vivo study demonstrates that all biopsy techniques are applicable to detect targets with approximately 80% sensitivity and median precision of 2–3 mm. Thus, detec-tion of clinically significant cancer might not be influenced by the choice of biopsy system when an experienced urolo-gist performs the procedure with an exact image fusion and biopsy sampling. However, patients with large prostate vol-umes might benefit from a TRB with elastic image fusion. When MRI reveals small or anterior localized lesions, TRB with elastic image fusion or TPB seems to be superior in detection compared to TRB with rigid image fusion. Fur-ther studies will be necessary to compare the accuracy in a clinical setting.

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