A Novel Stereotactic Prostate Biopsy System Integrating Pre-Interventional Magnetic Resonance Imaging and Live Ultrasound Fusion

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Abbreviations and Acronyms

2D = 2-dimensional
3D = 3-dimensional
ADC = apparent diffusion coefficient
DCE = dynamic contrast enhanced MRI
DICOM = Digital Imaging and Communications in Medicine
DRE = digital rectal examination
MR = magnetic resonance
MRI = MR imaging
PC = prostate cancer
T1w = T1-weighted
T2w = T2-weighted
TRUS = transrectal US
TSE = turbo fast spin-echo
US = ultrasound

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Purpose: We developed an effective way to precisely diagnose prostate cancer using a novel prostate biopsy system that integrates pre-interventional magnetic resonance imaging with peri-interventional ultrasound for perineal navigated prostate biopsy.
Materials and Methods: A total of 106 men with findings suspicious for prostate cancer (median age 66 years, prostate specific antigen 8.0 ng/ml and prostate volume 47 ml) underwent multiparametric 3 Tesla magnetic resonance imaging. Suspicious lesions were marked and data were transferred to the novel biopsy system. Using a custom-made biplane transrectal ultrasound probe mounted on a stepper we gathered 3-dimensional ultrasound data and fused them with magnetic resonance imaging data. As a result, suspicious magnetic resonance imaging lesions were superimposed over the transrectal ultrasound data. Three-dimensional biopsy planning was done, including systematic biopsies. Perineal biopsies were taken under live ultrasound guidance and the precise site of each biopsy was documented in 3 dimensions. We evaluated feasibility, safety and cancer detection.
Results: Prostate cancer was detected in 63 of 106 patients (59.4%). Magnetic resonance imaging findings correlated positively with histopathology in 71 of 103 patients (68.9%). In magnetic resonance imaging lesions marked as highly suspicious, the detection rate was 95.8% (23 of 24 cases). Lesion targeted cores had a significantly higher positivity rate than nontargeted cores. The procedural targeting error of the first 2,461 biopsy cores was 1.7 mm. Regarding adverse effects, 2 patients experienced urinary retention and 1 had a perineal hematoma. Urinary tract infections did not develop.
Conclusions: Perineal stereotactic prostate biopsies guided by the combination of magnetic resonance imaging and ultrasound enable effective examination of suspicious magnetic resonance imaging lesions. Each biopsy core taken is documented accurately for its location in 3 dimensions, enabling magnetic resonance imaging validation and tailored treatment planning. The morbidity of the procedure was minimal.

Key Words: prostate, prostatic neoplasms, biopsy, ultrasonography, magnetic resonance imaging

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PROSTATE cancer is the most common solid tumor and the second leading cause of male cancer death in the United States.[1] A key challenge for PC therapy is to precisely diagnose tumor lesions. TRUS guided systematic biopsy represents the standard of care for prostate sampling. According to current guidelines initial biopsies should include 12 cores[2] and result in a detection rate of between 24% and 44%.[3–5]

Precise information on tumor grade, stage and site is mandatory to counsel men with PC since these factors greatly influence treatment decisions. To prevent overtreatment for low risk PC and decrease treatment related morbidity focal therapy may likely be the future method of choice for men with localized disease who do not elect active surveillance protocols.[6,7] The key challenge of focal therapy for PC is to identify index lesions while its Achilles' heel is the need to exactly localize lesions in 3 dimensions. In their landmark studies Barzell and Melamed,[8] and Onik et al[9] described perineal prostate mapping biopsies as an appropriate method for optimal staging of localized PC. However, mapping biopsies requires a high number of cores per patient. After lesions are diagnosed direct export of 3D biopsy data to treatment systems such as high intensity focused US or cryotherapy is highly desired to enable and support focal therapy.

Multiparametric MRI allows for excellent soft tissue resolution and can detect PC with 73% sensitivity and 89% specificity.[10] However, the use of MRI in PC management is still controversial.[11] MR guided biopsies are not feasible in clinical routine due to limited availability, high cost, decreased ergonomics and long intervention time.[12–14] Thus, a combination of US and MRI might result in a practicable alternative. Such approaches have been reported,[15–19] typically as prototypes or at the experimental stage. The main drawback of these systems is that they use delicate electromagnetic tracking, which is highly susceptible to metallic and magnetic interference, decreasing precision.

In this context we describe the development of the novel BiopSee® prostate biopsy system, which integrates pre-interventional MRI data with peri-interventional US for perineal prostate biopsy. To our knowledge this is the first platform available for clinical routine that integrates imaging, TRUS/MRI fusion, biopsy planning, perineal targeting and 3D mapping into a single system, providing a complete clinical picture of cases suspicious for PC at 1 procedure.

PATIENTS AND METHODS

After receiving ethics committee approval and written informed consent we performed biopsy in a prospective cohort of 106 consecutive men with findings suspicious for PC, including median age 66 years, prostate specific antigen 8.0 ng/ml and prostate volume 47 ml (table 1). Of these patients 49 (46.2%) had already undergone negative TRUS guided biopsies. Ten patients (9.4%) had known low risk PC under active surveillance, 1 underwent biopsy for suspected local recurrence after radical prostatectomy and 46 (43.4%) were examined for the first time. According to local standards all patients were treated with perioperative chinolone antibiotics.

Multiparametric MRI

All MRI was performed using a 3.0 Tesla Magnetom® Trio MR scanner without an endorectal coil. Localizer sequences were obtained first to plan T2w TSE sequences. For lymph node staging a transverse T1w turbo echo sequence was used. High spatial resolution T2w TSE sequences in the transverse and coronal planes were then acquired with a resulting voxel size of 1.68 mm^3 (table 2). DCE was performed with a high spatial resolution T1w 3D gradient echo sequence with a voxel size of 3.84 mm^3 and a temporal resolution of 9.9 seconds. As the MR contrast agent, gadobutrol (0.1 mmol/kg) was administered. Three-D MR spectroscopic images were acquired by chemical shift imaging sequence and analyzed on a Syngo® work station. Spectral data were fitted manually over the corresponding morphological T2w images serving as the anatomical reference. For diffusion-weighted imaging standard 2D epi-sequences were used. All 7 sequences with different b values were used to calculate ADC maps in a mono-exponential fit. Total examination time was 36 minutes.

ADC maps and T2w images were assessed simultaneously and compared to the DCE and MR spectroscopy findings. All reports were evaluated by unblinded specialized uroradiologists (MR, PZ and HPS). Criteria used to rate T2w lesions as suspicious for PC were hypointense signal intensity with tuberose appearance, loss of anatom-

Table 1. *Patient data and results*

			No Prior Biopsy		Neg Prior Biopsy		Pos Prior Biopsy	
No. pts	106		46		49		11	
Median age (range)	66	(42–83)	65	(42–83)	66	(47–78)	67	(57–77)
Median ng/ml prostate specific antigen (range)	8.0	(0.5–441)	7.0	(1.36–441)	8.4	(0.5–49)	7.4	(1.3– 14)
Median ml prostate vol (range)	47	(6–160)	44.5	(16–124)	50	(16–134)	46	(6–160)
No. suspicious DRE	26		15		9		2	
No. highly suspicious MRI	24		12		9		3	
No. Ca pos (%)	63	(59.4)	31	(67.4)	22	(44.9)	10	(90.9)
No. pos biopsies/total No. (%)	280/2,461	(11.5)	147/1,070	(13.7)	80/1,159	(6.9)	53/232	(22.9)

Table 2. *Imaging parameters of the multiparametric MRI protocol of the prostate*

	TSE				
	T1w	T2w	2D Episequences	T1w 3D Gradient Echo Sequence	3D Spin Echo Chemical Shift Imaging
Repetition/echo time (msecs)	792/11	5,120/143	3,100/52	4.42/2.2	750/145
Flip angle (degrees)	90	90	—	15	90
Echo train length/epi factor	72	12	96	—	—
Av	2	4	5	0	3
b Value	—	—	0, 50, 100, 150, 200, 250, 800	—	—
Section thickness (mm)	5	3	3	1.5	6
Field of view (mm)	320	300	280	400	400
Resolution	1.1 × 1.0	0.8 × 0.7	2.2 × 2.2	1.6 × 1.6	6.0 × 6.0
Acquisition time (mins)	3:51	4:14	5:04	5:18	10:25

ical structures and asymmetrical appearance. Corresponding areas with a low ADC value were interpreted as highly suspicious. A rapid initial peak of the DCE curve and the presence of washout were also documented as probably malign.

System and Biopsy Procedure

The BiopSee system consists of a personal computer with an integrated US device and additional electronics to control US probe position and orientation (fig. 1). The probe has a custom-made biplane endorectal design with 150-degree transverse and 70 mm longitudinal field of view. Each array consists of 128 elements. The maximum available frequency is 8 MHz for the transverse plane and 10 MHz for the longitudinal plane.

BiopSee system software was written custom fit in a modular design. There is a kernel environment and each functional procedure step is mapped in a separate software module, including US device control, US image filtering, stepper encoder control, US data acquisition, DICOM data interface, volume fusion, contouring, biopsy planning, guiding and reporting, and a dedicated patient DICOM database.

The transperineal biopsy approach was chosen for several reasons. The most important reason was to overcome inaccurate manual positioning of the needle guide and prostate deformation by TRUS probe coronal and sagittal movement. Additional benefits include a decreased infection rate and preservation of the integrity of Denonvilliers' fascia for possible future intervention.

During the procedure the US probe is placed on a custom-made mechanical stepper with 2 df, that is one can adjust probe depth in the patient rectum and probe rotation along its main axis. Movement and rotation are tracked by 2 built-in encoders connected to the personal computer. Movement resolution is 0.1 mm and 0.1 degree. The stepper is fixed to the operating table. As a result, any

Figure 1. BiopSee system consists of personal computer with integrated US device and additional electronics to control position and orientation of US probe. Probe has custom biplane endorectal design and is placed on custom mechanical stepper. Device movement is tracked by 2 encoders with resolution of 0.1 mm and 0.1 degree.

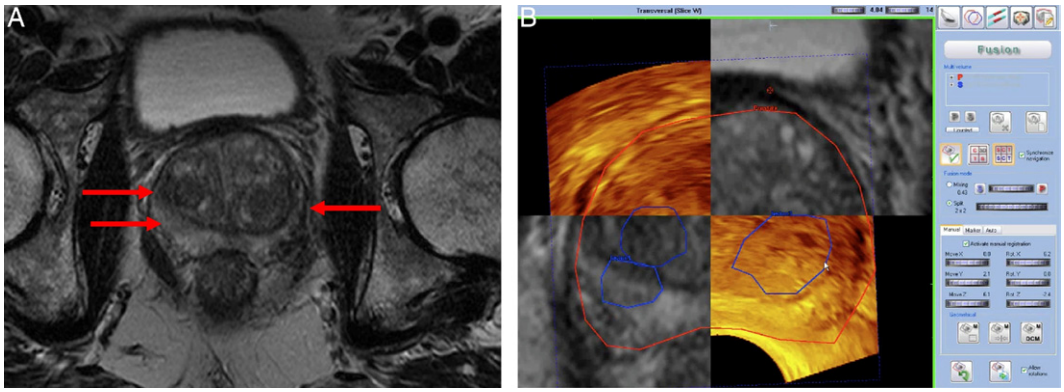

Figure 2. *A,* multiparametric MRI was done to detect suspicious lesions. Regions of interest were marked on high spatial resolution T2w TSE sequences in transverse plane. In this patient note 1 highly suspicious area in right peripheral zone and 2 questionable lesions in right and left transition zones, respectively. MRI and US data 3D registration was achieved by custom software under simultaneous visualization of axial, coronal and sagittal planes. *B,* axial screenshot shows MRI (gray areas) and TRUS (orange areas) data.

prostate plane can be imaged with high accuracy and reproducibility, which is impossible with freehand probe movement. For needle insertion a template guide is attached to the stepper.

During intervention 3D US is acquired first by recording a series of transversal 2D images while moving the probe cranial to caudal, resulting in a 3D data set. Patients were placed under light general anesthesia using a larynx mask.

T2w MR images with marked lesions are imported via the DICOM interface, and 3D US and MRI are then fused together via an automated algorithm or manually under simultaneous visualization of the axial, coronal and sagittal planes. This allows the transfer of lesions marked on the diagnostic MRI over the intraoperative US data set (fig. 2). Biopsy cores are then placed virtually within the 3D data set (fig. 3).

Depending on lesion size 2 to 6 targeted biopsies are taken from each MRI suspicious region. Systematic biopsies of the peripheral zone of the prostate and 2 transition zone biopsies are also placed. Depending on prostate size 12 to 36 biopsies are planned. This first phase of the approach (3D US acquisition, MRI fusion and core planning) is typically completed within 10 minutes.

During the following phase the user selects the desired biopsy cores 1 after the other and first navigates the US probe to that position, ie the US transducer is rotated until the longitudinal plane crosses the virtual needle insertion line. The physician then inserts the needle under continuous longitudinal US guidance (fig. 4). Due to a long longitudinal crystal array the needles are visible immediately when entering the perineum and long before penetrating the prostate capsule. The US image is overlaid by organ and lesion contours as well as by the planned needle trajectory. Thus, real-time navigation is established in a way that deviations from the target become instantaneously visible on the screen and can be corrected early, enabling needle positioning with high accuracy. Organ shifts during needle insertion are equally visible and can be adjusted as needed.

After each biopsy the exact needle position is manually registered and stored with orientation data (2D and 3D topograms, longitudinal and transverse US views) for documentation purposes. The system can then calculate the difference between planned and actually performed 3D core positions (procedural targeting error).

Statistical Analysis

Data were collected in Excel®. Descriptive statistical analysis was done using Prism®.

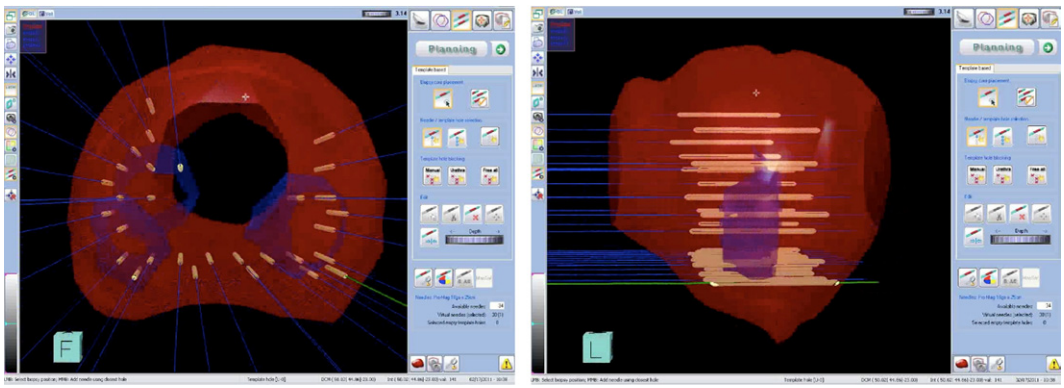

Figure 3. Biopsy cores were planned virtually in 3D data set using MRI and TRUS data. Biopsies were taken from suspicious lesions

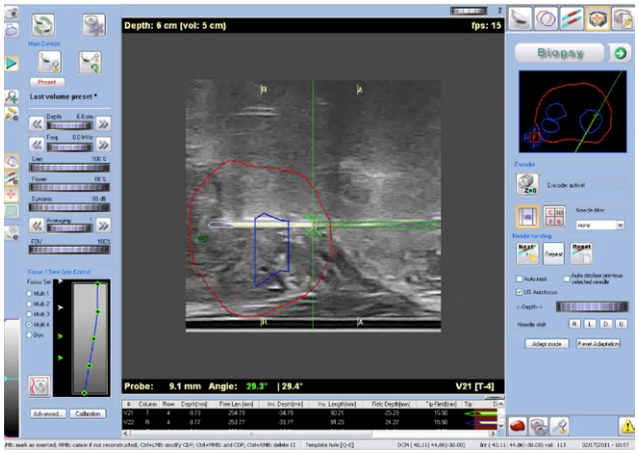

Figure 4. Biopsy needle inserted under continuous longitudinal US guidance. US image was overlaid by organ and lesion contours and planned needle trajectory to enable real-time navigation so that deviations from target were immediately visible on screen and could be corrected. After each biopsy, needle position and orientation data were stored for documentation.

RESULTS

Stereotactic biopsies were performed by 1 of 4 urologists (BAH, THK, IVP or TS). The median number of biopsies per patient was 24 (range 12 to 36). In the first 10 men the whole procedure, including planning and navigation, required around 60 minutes. Later intervention time, including anesthesia, was about 30 minutes.

In 63 of 106 consecutive patients (59.4%) biopsy samples revealed PC (table 1). Of 46 men undergoing initial biopsy cancer was diagnosed in 31 (67.4%). Results in 49 patients undergoing rebiopsy without a previous cancer diagnosis were positive in 22 (44.9%). The single patient with suspected local recurrence was diagnosed with a high risk tumor in all lesion directed biopsies. In the 10 men undergoing scheduled rebiopsy during active surveillance PC was detected in 9, of whom 6 showed progression, leading to a recommendation for active treatment. The patient without cancer on biopsy initially had incidental T1a PC.

On multiparametric 3 Tesla MRI 24, 42 and 37 cases were diagnosed as highly, questionably and not suspicious for PC, respectively. Three MRI reports from radiologists elsewhere were not evaluated due to incomplete multiparametric data. Our results showed a positive correlation between histopathology and MRI findings (PC vs benign disease on biopsy) in 71 of 103 patients (68.9%). In MRI lesions marked highly suspicious the tumor detection rate was 95.8% (23 of 24). When combining MRI lesions marked highly and questionably suspicious, the tumor detection rate was 71.2% (47 of 66). Of 37 cases 24 (64.9%) considered not suspicious for PC on MRI were also negative on biopsy. Suspicious DRE did not match MRI findings well with positive DRE in 8 of 24 cases (33%) of highly suspicious lesions. However, clinical examination provided additional information for overall tumor prediction in 22 of 26 cases.

After evaluating 410 single cores from lesions that were highly or questionably suspicious on MRI PC was detected in 101 (24.6%). In contrast, only 179 of 2,051 additional systematic biopsies (8.7%) were positive (chi-square test $p < 0.0001$). The rate of positive cores from highly suspicious areas was 44.4% (63 of 142).

When comparing the virtually planned biopsy trajectory and the manually documented 3D needle position of each single biopsy core taken, the average ± SD procedural targeting error of the first 2,461 biopsy cores was 1.7 ± 1.7 mm. The highest deviation between planned and registered coordinates was in the coronal plane (mean 2.86 ± 2.42 mm), followed by the sagittal (1.36 ± 0.73 mm) and axial (0.92 ± 0.63 mm) planes.

Regarding adverse effects, 2 patients experienced urinary retention requiring short-term catheterization and 1 had a significant perineal hematoma. No urinary tract infections developed.

DISCUSSION

In our first 106 consecutive patients undergoing initial prostate biopsy with a mean of 24 cores taken cancer was detected in 31 of 46 (67.4%). Similar to our results, Taira et al recently reported a 76% detection rate in men undergoing transperineal template guided mapping biopsies but using a mean of 55 cores per patient.[20] When comparing our patient characteristics with those in the literature, our population seems representative of an average to high risk group of men referred for initial biopsy.[4,21] The diagnostic improvement of 67.4% PC detection on initial biopsies compared to approximately 40% detection rate of conventional 10 to 18-core TRUS biopsies was most likely a result of integrating MRI information. This hypothesis is supported by the significantly higher PC detection rate in lesion directed vs systematic cores (24.6% vs 8.7%, $p < 0.0001$). However, patient selection also might have influenced the PC yield.[22] A randomized, multicenter trial is planned to evaluate adding targeted cores to systematic biopsies.

The transperineal biopsy approach allows good access to all prostate regions and decreases the prostate deformation that occurs with the coronal and sagittal movement of the TRUS probe that is needed to perform transrectal biopsy. Fusion of 3 Tesla MRI data, which is acquired without an endorectal coil, with 3D TRUS images was easy since we noted no

major differences in prostate configuration on TRUS and MRI. Regarding the intervention time of around 30 minutes, prostate biopsies using the BiopSee system are between standard TRUS and MR guided biopsies.[23] In our opinion the heavier protocol compared to that of TRUS biopsy is warranted due to the more complete pretreatment clinical picture, which potentially has a significant impact on PC management, especially in regard to the emergence of focal therapy. Since men in Germany prefer analgosedation for prostate biopsy,[24] general anesthesia was not a major concern. Compared to transperineal template guided prostate mapping biopsies, after which up to 40% of patients are catheter dependent for a few days,[25] the morbidity of the technique described is minimal.

In the 49 patients who underwent rebiopsy for suspected PC our diagnostic yield of 44.9% competes with that rate of purely MR guided biopsies. Engelhard et al recently reported a 38% detection rate for MR guided rebiopsies.[26] On the other hand, for TRUS saturation rebiopsy a detection rate of merely 20% to 30% was reported.[27,28] Although it is superior to TRUS, MR guided biopsy approaches have multiple disadvantages. They have limited availability, cannot be done in real time, and are complex and costly to perform due to the requirements of MR compatible equipment.[14,23] Thus, this technique of prostate biopsy is not feasible for routine use, especially not by urologists.

Looking at the accuracy of MRI findings and histopathology, our result of 68.9% unmistakably shows that MRI still requires improvement. Although dedicated uroradiologists evaluated about 2,000 images per patient, further refinement of MRI diagnostics is needed to ensure more reliable differentiation between tumors and benign disease such as prostatitis. Since BiopSee provides exact documentation of the site of each individual biopsy, MRI data may be validated using histopathology from single cores, which can be correlated to fused MR images. Until more studies are completed, such as the recent series by Turkbey et al,[29] we elected to take saturation biopsies as well as MRI targeted stereotactic cores to avoid under diagnosing high risk tumors. In turn, over diagnosis can easily be managed by active surveillance.

Focal treatment for low risk prostate tumors will likely be a much sought future option to decrease treatment associated morbidity.[6,7] To be able to treat index lesions precise diagnostics are mandatory to exactly localize PC. The system described seems appropriate for such tasks. The overall mean targeting error was 1.7 ± 1.7 mm. The highest deviation was observed in the coronal plane since the prostate is pushed cranial while inserting the needle. This movement will be addressed by automatic flexible registration of the prostate contour, which is currently under investigation. Documentation of each single biopsy position is automatically provided in a 3D prostate model and the generated database of DICOM files can be exported and used for scheduled rebiopsies and treatment planning.

CONCLUSIONS

Perineal stereotactic prostate biopsies guided by combined multiparametric MRI and US enable excellent examination of the prostate and efficient targeting of suspicious MRI lesions. The higher complexity compared to that of standard transrectal biopsy is justified by a better detection rate and more comprehensive staging. Each biopsy site is documented precisely in 3 dimensions, which may guide future focal treatment. Also, the resulting data might be used to validate MRI, enabling more precise interpretation of MRI findings. At the same time procedure morbidity was minimal.

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