

Safety and Feasibility of Direct Magnetic Resonance Imaging-guided Transperineal Prostate Biopsy Using a Novel Magnetic Resonance Imaging-safe Robotic Device

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OBJECTIVE	To evaluate safety and feasibility in a first-in-human trial of a direct magnetic resonance imaging (MRI)-guided prostate biopsy using a novel robotic device.
METHODS	MrBot is an MRI-safe robotic device constructed entirely with nonconductive, nonmetallic, and nonmagnetic materials and developed by our group. A safety and feasibility clinical trial was designed to assess the safety and feasibility of a direct MRI-guided biopsy with MrBot and to determine its targeting accuracy. Men with elevated prostate-specific antigen levels, prior negative prostate biopsies, and cancer-suspicious regions (CSRs) on MRI were enrolled in the study. Biopsies targeting CSRs, in addition to sextant locations, were performed.
RESULTS	Five men underwent biopsy with MrBot. Two men required Foley catheter insertion after the procedure, with no other complications or adverse events. Even though this was not a study designed to detect prostate cancer, biopsies confirmed the presence of a clinically significant cancer in 2 patients. On a total of 30 biopsy sites, the robot achieved an MRI-based targeting accuracy of 2.55 mm and a precision of 1.59 mm normal to the needle, with no trajectory corrections and no unsuccessful attempts to target a site.
CONCLUSION	Robot-assisted MRI-guided prostate biopsy appears safe and feasible. This study confirms that a clinically significant prostate cancer (≥ 5 -mm radius, 0.5 cm^3) depicted in MRI may be accurately targeted. Direct confirmation of needle placement in the CSR may present an advantage over fusion-based technology and gives more confidence in a negative biopsy result. Additional study is warranted to evaluate the efficacy of this approach. UROLOGY ■■■: ■■■-■■■, 2017. © 2017 Elsevier Inc.

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Prostate cancer (PCa) is most commonly detected as a result of prostate-specific antigen (PSA) screening with a subsequent transrectal ultrasound (TRUS)-guided biopsy. Although PSA screening has led to reduced PCa-specific mortality,¹ concerns exist regarding both the overdiagnosis of indolent disease² and the underdiagnosis of high-grade disease.³ Additionally, TRUS-guided biopsy is associated with both low sensitivity and a high false-negative rate.^{4,5}

While traditional biopsy relies on PCa-blind, untargeted 12-core biopsies, advances in multiparametric magnetic resonance imaging (mpMRI) have allowed visualization of lesions within the prostate.⁶ Consequently, mpMRI has increasingly been adopted as a tool for PCa detection⁷ and staging,⁸ and has been used more recently for biopsy targeting. Magnetic resonance imaging (MRI)-fusion biopsy,

a technology in which a preacquired MRI is registered (fused) with TRUS, showed an increased diagnosis of high-risk PCa and a decreased detection of low-risk cancers.⁹ Results of MRI-fusion biopsy are encouraging and the technology is a substantial advance over the TRUS alone. Although studies have evaluated the correlation of fusion biopsy findings with whole-gland radical prostatectomy specimens,⁹ the accuracy of fusion biopsy in targeting cancer-suspicious regions (CSRs) in real time is unknown. Therefore, it remains unclear if this technology is sufficiently accurate to consistently target significant PCa lesions.

MRI fusion is subject to several technical limitations. Gland shape compression, temporal differences, and patient position differences between the preacquired MRI and interventional TRUS can cause registration misalignment.¹⁰ In MRI-fusion systems, confirmation of needle placement is confirmed with ultrasound in the absence of real-time MRI. These limitations may contribute to biopsy targeting errors, but it is impossible to know if or when this happens as there is no real-time visual confirmation of needle placement with MRI.

An alternative that circumvents fusion is direct MRI-guided biopsy, in which CSR targeting, needle guidance, and postbiopsy targeting confirmation are verified under MRI. MRI-guided in-bore biopsies are challenging, secondary to limited access to the patient within the bore of the scanner, and manual instrument handling, adjustments of the needle guide angulation, and needle insertion depth, which are prone to imprecisions.^{11,12} A solution to this problem is the use of robotic devices designed to operate in the space and environmental restrictions inside the magnetic resonance scanner. In this pilot study, we evaluate a direct, in-gantry transperineal prostate biopsy using a novel robotic device (MrBot)¹³⁻¹⁷ for safety and feasibility.

METHODS

Study Design

The present study was a first-in-human safety and feasibility study of the MrBot investigational device for direct MRI-guided transperineal prostate biopsy. Technical details regarding the robotic system, regulatory clearance, and image guidance have been previously published.¹⁸ The device was approved by the Food and Drug Administration for the study and our institutional review board approved an initial safety and feasibility study limited to 5 patients. Inclusion criteria were men between ages 35 and 75, a prior negative 12-core biopsy, and at least one of the following features: (1) a PSA level of ≥ 5 ng/mL and a prostate volume of ≤ 50 cc, (2) a PSA density of ≥ 0.2 ng/mL/cc, (3) a percent free PSA of $\leq 10\%$, (4) a PSA velocity of >0.5 ng/mL/year, or (5) a high-grade prostate intraepithelial neoplasia or atypia on a previous biopsy. Patients were excluded if they had bleeding problems, MRI-incompatible implants, a previous rectal surgery, or a previous pelvic irradiation. Even though this safety and feasibility study was not designed for clinical significance, patients with a CSR on independently

available mpMRI were selected for the study to increase the likelihood of visualizing CSRs at the time of the intervention. CSRs were scored on a 5-point Likert scale (1, highly likely benign; 2, likely benign; 3, indeterminate; 4, likely malignant; and 5, highly likely malignant), as previously described.^{19,20} The trial was registered at clinicaltrials.gov (NCT02080052).

MRI Protocol

On the day of the biopsy, the patient underwent a shorter MRI with T2-weighted fast spin-echo images: repetition time and echo time = 3170 and 80 ms; slice thickness, 4 mm; interslice gap, 0-1 mm; matrix, 384×288 ; field of view, 40×40 cm; frequency direction: anteroposterior; number of excitations = 2, and "distortion correction" parameter ON. CSRs were identified and used for targeting in addition to sextant locations.

Device and Procedure

MrBot is an MRI-safe²¹ robotic device constructed with non-magnetic and dielectric materials and powered by a pneumatic step motor.¹⁶ The robot is electricity free, using air for actuation and light for the sensors. The device is mounted on the MRI table beside the patient while in the left lateral decubitus position^{13,14} (Fig. 1). To prevent patient motion, for this safety and feasibility trial the patient was placed under general anesthesia. A small (1 cm) perineal skin incision was made. To gain room for the robot, the patient was positioned with the back as close as possible to the magnetic resonance bore. The robot was placed on the table so that the nozzle of the needle guide was placed superficially through the incision. The robot was secured with vacuum-powered suction cups on the table, at an angle that pointed the needle guide approximately toward the prostate.

A 3-T whole-body scanner with a 60-cm bore size (TrioTim; Siemens Medical Solutions, Malvern, PA) was



Figure 1. The MrBot robot is positioned in the MRI gantry next to the patient in the left lateral decubitus position. MRI, magnetic resonance imaging. (Color version available online.)

used with a surface body matrix coil wrapped over the pelvis and an optional endorectal eCoil (Medrad, Warrendale, PA). Images were acquired and the robot was registered to the image space based on registration markers built in the robot structure. Biopsy target points, including the CSR, were defined in the MRI. One by one, the robot positioned and oriented the needle guide straight on target. The depth of needle insertion was also automatically set by adjusting the location of a depth limiter to the point selected in the image corresponding to the center of the core slot of the needle.

Two types of needles were used in the study, both manufactured by Invivo, Pewaukee, WI: 9896-032-02861 (11528), 18Ga × 150mm Semi-Automatic Biopsy Gun, and 9896-032-05281, 18Ga × 175mm Fully Automatic Biopsy Gun. A transperineal biopsy was performed manually through the guide up to the depth limiter. Confirmation imaging with True FISP (true fast imaging with steady-state precession) of the needle was acquired. The procedure then cycles to the next selected biopsy target.

Analysis

The primary objective of the present study was to evaluate the safety and feasibility of an MRI-guided robot-assisted transperineal prostate biopsy. The outcome variables of the study include clinical measures such as the patient characteristics, times for several steps of the procedure (patient positioning, anesthesia, device setup, imaging, robot registration, biopsy planning, and biopsy procedure), number of biopsy sites, complications, patient discomfort (1-5, 1—none), pain level (1-5, 1—none), and overall satisfaction (1-5, 1—completely satisfied) (logged at the end of the procedure and 24 hours following the procedure). Patient characteristics include the number of prior negative biopsies acquired with TRUS, the number of CRSs observed in the previously acquired MRI, and the CSR score from the same MRI.

Outcome variables related to the operation of the robotic device include the number of unsuccessful attempts to target a site, the number of trajectory corrections to target a site, and targeting errors. Targeting errors were measured in MRI as the distance between the actual biopsy core center and the target point, as a 3D vector, and also in a plane normal to the needle. Accuracy and precision were calculated as usual, based on the mean and the standard deviation of the respective errors.

Table 2. Outcome variables

		Mean (SD)
Times (min)	Patient positioning and anesthesia	70 (26)
	Device setup	8 (3)
	Imaging	50 (18)
	Robot-to-image registration	8 (6)
	Define biopsy locations	6 (3)
	Biopsy time per site	10 (1)
	Total clinical time	208 (30)
	Number of biopsy sites per patient	7.8 (1.30)
	Unsuccessful attempts to target a site	0
	Patient discomfort (1-5, 1—none)	1.6 (0.55)
	Pain level (1-5, 1—none)	1.2 (0.45)
	Overall satisfaction (1-5, 1—completely satisfied)	1.2 (0.45)

SD, standard deviation.

RESULTS

Five men underwent biopsy using MrBot. The mean age was 66.4 years (range 55-72), and the mean PSA level was 22.4 ng/dL with an average prostate size of 76.6 cc. Patient characteristics and biopsy results are listed in [Table 1](#). All patients tolerated the procedure well. Post procedure, 2 men experienced acute urinary retention that required Foley catheter insertion, with no other complications and no subsequent adverse events. Both patients subsequently passed a trial of voiding 3 days after the procedure without further interventions.

Clinically related outcome variables are shown in [Table 2](#). The mean number of biopsies per patient was 7.8 (median 8), and there were no unsuccessful attempts to target a site. The mean patient discomfort, pain level, and overall satisfaction were 1.6, 1.2, and 1.2, respectively.

The mean total clinical time for the procedure was 208 minutes, and the time decreased with each subsequent patient ([Supplementary Fig. S1](#)). In case 3, the MRI scanner shut down at the beginning of the procedure for an unknown cause, adding time to the procedure.

An endorectal coil was used only on the first patient, and no endorectal coil was used in the subsequent 4 cases. The first case was performed with the semiautomated biopsy needle. Six biopsy sites were targeted and 3 trajectory corrections were necessary. The accuracy was 14.78 mm and the precision was 3.82 mm. Needle deflection from a straight path was pronounced.

Table 1. Patient size, clinical and imaging characteristics, and biopsy result

Patient	Size				PSA	Prostate Size (cm ³)	Prior			Biopsy Result
	AP (cm)	TV (cm)	AP + TV (cm)	Weight (kg)			Negative Biopsies	CSR	CSR Score	
1	24	40	64	89	43.3	148	2	2	3	Negative
2	21	35	56	68	29	47	2	1	4	Positive
3	19.2	36.6	55.8	67	4.8	44	2	2	4	Positive
4	22.5	38.5	61	91	8.9	42	1	1	3	Negative
5	19.9	38.6	58.5	79	26	102	3	1	3	Negative

AP, anterior-posterior; CSR, cancer-suspicious region; PSA, prostate-specific antigen; TV, transverse.

For the subsequent cases, the needle was changed to the fully automated type. Moreover, near the midpoint of the insertion stroke, the needle was rotated 180° about its axis to compensate for lateral deflections caused by the beveled point. In the final 4 cases, the accuracy and the precision of targeting over 30 biopsy sites were 2.97 and 1.50 mm, respectively, in 3D, and 2.55 and 1.59 mm, respectively, in a plane normal to the needle, with no trajectory correction.

Biopsies confirmed the presence of a clinically significant cancer in 2 patients.

Patient 2 was a 70-year-old man with a 47-cc prostate and a PSA level of 29 ng/dL. MRI demonstrated a CSR score of 4 in the right transition zone. Targeted biopsy with MrBot demonstrated Gleason 4 + 3 = 7 (grade group 3) PCa in 2 cores. This patient subsequently underwent radical prostatectomy that demonstrated 4 + 3 = 7 (grade group 3) PCa with extraprostatic extension, with negative margins (pT3N0). The patient had an undetectable PSA at the last follow-up.

Patient 3 was a 64-year-old man with a 44-cc prostate and a PSA level of 4.8 ng/dL. MRI demonstrated a CSR score of 4 in the left anterior apex. Targeted biopsy with MrBot demonstrated Gleason 5 + 4 = 9 (grade group 5) in 2 cores, Gleason 4 + 4 = 8 (grade group 4) PCa in an additional core, and high-grade prostatic intraepithelial neoplasia in a core. Preprocedure mpMRI images, as well as intraprocedural targeting and confirmation images, are shown in Figure 2. The patient subsequently underwent radical prostatectomy and was found to have Gleason 4 + 5 = 9 (grade group 5) PCa with extraprostatic extension,

bilateral seminal vesicle invasion, positive margins, and negative lymph nodes (pT3bN0R1). The patient underwent adjuvant radiotherapy with androgen deprivation and had an undetectable PSA at the last follow-up.

In patient 1, needle deflections were pronounced, the targeting accuracy was low, and the biopsy result was benign. The patient was subsequently diagnosed with a high-grade PCa in the anterior transition zone following a repeat mpMRI. The patient underwent radical prostatectomy, revealing a dominant nodule 3 + 5 = 8 in the anterior right and left prostate base, mid, apex. The patient also had a left anterior extraprostatic tumor extension (pT3a).

DISCUSSION

The present study was designed to evaluate the safety and feasibility of direct MRI-guided robot-assisted transperineal prostate biopsy. We found that this technology is feasible and safe, with transient urinary retention as the only adverse side effect. This finding was not unsurprising, as acute urinary retention is a known complication of perineal prostate biopsy. Buskirk et al reported an 11.5% rate of retention after transperineal prostate biopsy and found that the number of biopsies and the prostate size were predictors of retention.^{22,23}

The main critique of direct MRI-guided interventions so far is the lengthy procedure time.²⁴ This technique collates several procedures that are normally done independently, including the anesthesia and the MRI, which are inherently slow. By itself, the biopsy procedure time or site was on the order of 10 minutes. Overall, a decreasing total

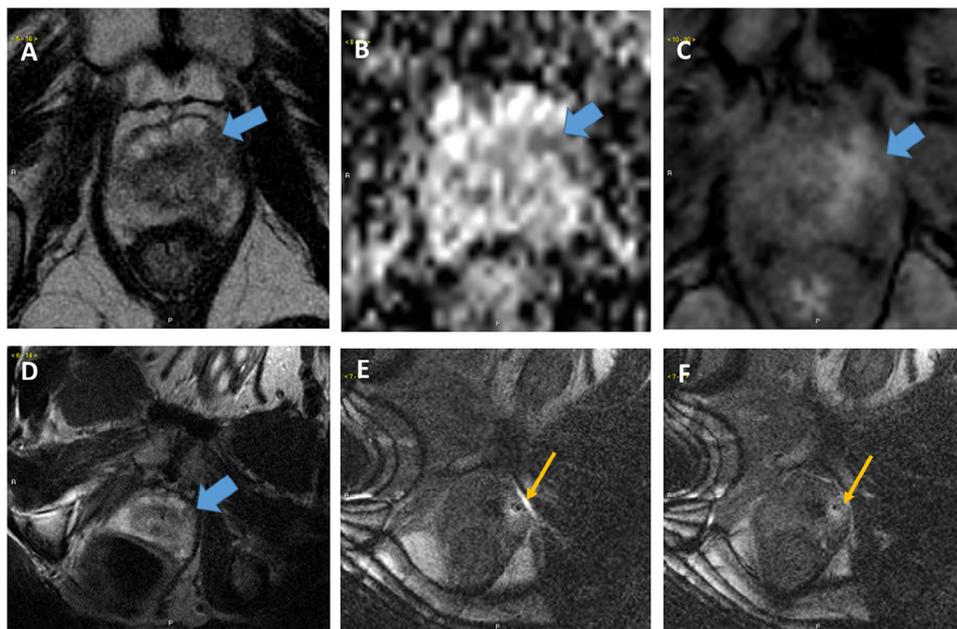


Figure 2. Patient 3. Prebiopsy images (A-C) demonstrate (A) T2-weighted, (B) diffusion-weighted imaging-apparent diffusion coefficient, and (C) dynamic contrast-enhanced sequences of the left-apical cancer-suspect regions. Intraprocedural image (D-F) demonstrates (D) T2-weighted image acquired during the procedure in the left decubitus position, (E) needle entering the prostate, and (F) needle in the target lesion. The blue arrows point to cancer-suspect regions while yellow arrows represent the needle. R, right; P, posterior. (Color version available online.)

time trend was observable over the 5 cases, but it is unknown to what level these may be reduced with further experience and technology improvements. In this safety and feasibility study, we opted for general anesthesia to reduce problems related to patient motion. A recent similar study²⁴ reported the use of intravenous procedural sedation and lower times.

Even though mpMRI was not used during the biopsy, PCa was still sampled at biopsy based on the T2-weighted images alone. Overall, PCa was detected in 2 patients (40%) and missed in 1 patient (20%). The missed case was our first case when targeting errors were large and needle deflection was pronounced. Even so, this detection rate is on par with longitudinal studies of repeat biopsy after an initial negative biopsy.^{25,26} Ploussard et al reported the detection of PCa on subsequent biopsies as 16.7% after the second biopsy, 16.9% after the third biopsy, and 12.5% after the fourth biopsy.²⁵ Similarly, Gann et al found an increasing number of biopsies associated with lower risk of detection, whereas elevated PSA levels were associated with a higher risk of detection.²⁶

An important outcome parameter of the study is the measurement of targeting accuracy, as this is an unknown parameter with fusion methods. The robot was capable of 2.55-mm accuracy. For PCa, the required accuracy is probably <5 mm, because a clinical significant tumor (0.5 cm³) has a 5-mm radius if spherical. However, staying within the 5-mm radius is very difficult. Targeting errors include several, often cumulative components.¹⁸ In our case 1, the errors were on the order of 15 mm. A problem that many others also confronted is that needle deflection errors are sizeable.²⁷ We have been able to cope with that by using a fully automated biopsy needle and rotating the needle 180° about its axis near the middle of the insertion stroke.²⁸

The achieved MRI-based targeting accuracy of 2.55 mm is novel. The most recent similar direct MRI-guided clinical trial²⁴ was performed on a large population of 30 patients, but unfortunately, the targeting accuracy data were not reported. These data are also missing for the fusion methods. As such, the present study demonstrates that the smallest clinically significant PCa tumors may be accurately targeted.

If the largest or most identifiable CSRs in MRI are the most clinically significant ones, then accurate targeted biopsy will (1) reduce the randomness that yields clinically insignificant cancer detection and (2) increase the likelihood of sampling the most advanced CSR, reducing the underdiagnosis of a potentially lethal cancer. Currently this is unknown. The accurate biopsy method may help validate PCa imaging methods.

Relative to fusion biopsy, which has no quality control relative to the imaging method used to identify the CSR, direct (imaged) confirmation of needle insertion in the CSR may give more confidence in a negative biopsy result. Fusion biopsy, however, is a nondisruptive advance over the standard TRUS technique, and remains to be tested if the additional accuracy is helpful.

The main limitations of our study are its small sample size that was required by the institutional review board to demonstrate safety before increasing the enrollment, and the basic MRI, rather than mpMRI, used in this initial trial. Additionally, as this is the initial report on a new technique, there is likely a learning curve that is not yet overcome in this series. It is yet unknown if using mpMRI to guide biopsy will increase the rate of significant PCa detection.

CONCLUSION

In this initial report of a robot-assisted direct MRI-guided prostate biopsy, the procedure appears safe and feasible, but currently lengthy. We demonstrate that it is possible to accurately target the smallest clinically significant PCa tumor depicted in MRI. A larger efficacy study is needed to define the role of this procedure in clinical practice.

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APPENDIX

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.urology.2017.07.010>.