



Comparison of Robotic and Manual Needle-Guide Templates in MRI-Guided Transperineal Prostate Biopsy

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Abstract

Purpose: Demonstrate the utility of a robotic needle-guidance template as compared to a manual template for in-bore 3T transperineal MR guided prostate biopsy.

Materials and Methods: This non-randomized two-arm trial included 99 cases of targeted transperineal prostate biopsies. The biopsy needles were aimed to suspicious foci in multiparametric 3T MRI using a manual template before a cut-off date or a robotic template after the date. The following data was obtained: the accuracy of average and closest needle placement to the focus, cancer yield, percentage of cancer volume in positive core samples, and time to complete the procedure.

Results: 56 cases were performed using the manual template, and 43 cases were performed using the robotic template. The mean accuracy of the best needle placement attempt was higher in the robotic group (2.39 mm) than the manual group (3.71 mm, $p<0.027$). The mean core procedure time was shorter in the robotic (90.82 min) than the manual group (100.63 min, $p<0.030$). Cancer yield was higher in robotic group ($p<0.018$).

Conclusion: The robotic needle-guidance template was useful in MRI-guided core biopsy of prostate cancer compared to the manual approach.

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Glossary of Abbreviations

3D Slicer	A software used to preplan the robot target coordinates
3T	3 Tesla A unit of measurement for magnetic field strength
BWH	Brigham and Women's Hospital
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine The software used to view and manipulate MR images
MRI	Magnetic resonance imaging
MR	Magnetic resonance
Open IGTLink	Open Network Interface for Image-Guided Therapy
PACS	Picture archiving and communication system
PSA	Prostate specific antigen A biomarker used to screen for prostate cancer. In general, a level of > 4.0ng/mL is an indication for further workup
TRUS	Transrectal ultrasound Another method used to image the prostate for biopsy collection

MRI-specific terminology

TR	Repetition time
TE	Echo time
FOV	Field of view
T1	A sequence with a short TR and a short TE; fat is bright and fluid is dark
T2	A sequence with a long TR and a long TE; fat and fluid both appear bright
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhanced sequence

Section 1: Introduction

Prostate cancer is the most common type of malignancy in men in the United States and the second leading cause of cancer deaths (1). The gold standard for diagnosis of prostate cancer is identification of a cancer-containing lesion on transrectal ultrasound (TRUS) guided biopsy of the prostate. However, many patients that are eventually diagnosed with prostate cancer have negative TRUS findings. In these cases, magnetic resonance imaging (MRI)-guided biopsy can be used to give the clinician a better view of suspicious foci (2, 3, 4).

MRI-guided biopsy has been proposed as an appropriate alternative to TRUS-guided biopsy in patients with rising prostate-specific antigen (PSA) values and clinical suspicion of prostate cancer despite negative ultrasound findings (2, 3, 4). MRI allows the clinician to better see the difference between the target lesion and the surrounding soft tissue structures as MRI provides better contrast between adjacent soft tissue structures. This helps clinicians better localize the lesion. MRI guidance also allows the clinician to get a clearer view of the biopsy needle so he or she can perform a targeted biopsy to the suspicious focus (5). Previous studies have found that MRI-guided biopsy results in a tumor detection rate of 51-59% (2, 6) compared to an estimated yield of 15-32% using TRUS alone (7, 8, 9). In men with at least one prior negative TRUS biopsy but high clinical suspicion of cancer, the rate of diagnosis from MRI-guided biopsy can be as high as 70% (10). This suggests that MRI-guided biopsy is a useful tool to diagnose cancer in patients that have strong clinical symptoms but cannot meet the official diagnostic criteria.

However, MRI has limitations of its own that make it difficult to widely use it to guide biopsy procedures. MRI is a lengthy and involved process compared to ultrasound, which can be done at the bedside. Patients must lie still within the scanner to ensure high quality images and access to the patient is limited within the scanner bore. The area of interest being imaged must be positioned at the center of the scanner bore. This means that the clinician must reach into the bore from the outside to acquire biopsy samples.

Currently, the majority of MRI-guided prostate biopsies are conducted either free hand or using a plastic template that supports the needle as the clinician inserts it into

the prostate. An emerging technology is the use of robotic devices that can align and deploy the needle without clinician intervention. A robotic device that functions inside the scanner bore can overcome the difficulty of maneuvering inside the scanner and allow the clinician to acquire high quality biopsy samples in less time. Since images are now viewed digitally, these robotic devices can be fiducially registered to the MRI scanner and can directly acquire the coordinates of the target lesion from the image processing software. This could potentially reduce human error in needle placement, make procedures shorter and yield better samples. Robotic devices also make it easier to access the patient inside the MRI scanner bore, which is narrow and does not leave a clinician much room to maneuver. A small robotic device can access the patient further inside the bore without needing to draw the patient outside of the bore (11, 12).

A number of MRI compatible robotic devices have been developed and applied clinically, aiming to improve transrectal biopsy under MRI guidance (13, 14, 15). Schouten et al. describe a robotic device that was able to achieve accuracy of 5.7 mm in transrectal prostate biopsies in 8 subjects. Another device developed by Krieger et al. (16) and clinically evaluated by Xu et al. (17) enrolled 24 subjects and reported targeting accuracy of 2.5mm. However, most of the robotic devices for transrectal biopsy reported in the literature have only been tested in phantom studies (11, 16, 18, 19) or on a very small number of clinical subjects. MRI compatible robotic devices can also be used for transperineal biopsies, but the studies reported are also limited to phantom or animal studies (20, 21, 22, 23, 24, 25, 26, 27, 28). Song et al. validated the accuracy of a transperineal biopsy robot in a phantom study (24). The transperineal approach allows better access to the anterior and apical regions of the prostate (9) and can be used in patients that cannot undergo TRUS guided biopsy because of total colectomy (25). The transperineal approach may also be advantageous for later use in focal therapy (9). Biopsy can also be transgluteal as reported by Zangos et al. in 19 subjects (29).

Despite recent increasing efforts to use robotic devices in MRI-guided biopsies, most of the studies presented thus far focus on validation of needle placement accuracy in phantoms or in a limited numbers of clinical subjects. Furthermore, while these studies validate that robotic devices can achieve an acceptable level of accuracy, they do not compare this accuracy to the current manual approach. There is an apparent paucity of

studies investigating the utility of robotic devices by comparing manual and robotic approaches.

The objective of this study is to provide a comprehensive comparison of MRI-guided manual and robotic biopsies with a group of subjects large enough to evaluate statistical significance. We validated the advantage of the MR compatible robot over a manual transperineal template by comparing time to complete procedures, accuracy of needle placement, and histopathologic outcomes. The intent is to see if the technological improvements made in the robot translate to improvements in clinical outcomes for patients. The selected outcomes are similar to those studied by other robot development laboratories in phantom experiments

This paper also serves as the first clinical report of a robotic device for transperineal MRI-guided biopsies that allows better access to the anterior and apical regions of the prostate (9) than the transrectal approach.

This study was conducted as a collaborative effort of many members of the Surgical Planning Laboratory. Sam Song, PhD designed and built the robotic template that was tested. Junichi Tokuda, PhD designed the manual template used as a comparison. Drs. Clare Tempany, Fiona Fennessey and Kemal Tuncali reviewed pre-operative images and determined the targets for sample collection. Dr. Tuncali performed the 99 manual and robotic procedures studied in this report. Olutayo Olubiyi did the final statistical analysis on the data set, which included log transforming some of the data. He wrote the section entitled “Statistical analysis” in Section 2 of this paper and the section on mixed retrospective-prospective cohorts in Section 4. He also provided substantial revisions to Section 3 (Results) in the final version of this paper. The author of this report, Gaurie Tilak, collected data on the procedures, did an initial statistical analysis with no log transformation, and determined which outcomes to report (with lots of guidance from Nobuhiko Hata, PhD, without whom this project would not exist). She also wrote the first draft of the manuscript, which was submitted after much revision from everyone noted above to the Journal of Magnetic Resonance Imaging in February 2014.

Section 2: Materials and methods

Patients

This retrospective cohort study was approved by the ethics review board of Brigham and Women's Hospital and written informed consent was obtained from all patients who enrolled. The study complied with the Health Insurance Portability and Accountability Act. All eligible patients had an abnormal PSA and had at least one MR suspicious lesion on 3T multiparametric MRI. Exclusion criteria were contraindications to MRI (cardiac pacemakers, brain aneurysm clips or significant claustrophobia) and cardiac disease with risk of silent ischemia.

Our patient cohort was similar to patients for whom an MRI-guided biopsy would be indicated. Many men are diagnosed with prostate cancer on the basis of TRUS-guided biopsy and never require further imaging studies. Patients were only selected for this study if they already had a negative TRUS biopsy but still had strong clinical suspicion of prostate cancer.

Ninety-seven consecutive patients were enrolled between December 2009 and June 2013 and underwent a total of 99 procedures. Two patients underwent two procedures each. Patients were assigned to manual or robotic procedure based on the date of their enrollment in the protocol. The 51 procedures done through September 2013 used the manual template. Forty-three procedures done after September 2012 were done using the robotic template. Four procedures done in October 2013 were switched to the manual method because the engineer that designed the robot needed to do maintenance work on it during that time. A single robot was used for all robotic procedures. The robot was checked regularly by the engineering team that designed it and required maintenance one time in October 2013.

The study officially commenced in September 2012 with the start of the robotic cases. At this point, most of the manual cases had already been completed. For the purposes of analysis, this was a retrospective study, despite some of the data collection being prospective. The patient inclusion criteria were the same as they were for MR-guided biopsy for manual cases.

Pre-biopsy evaluation

Three radiologists identified suspicious targets by reviewing pre-procedural MRI obtained in a 3-tesla (T) MRI (GE Signa HDx 3.0T MR scanner, GE Medical Systems, Milwaukee, WI). The pre-procedural imaging protocol included a T1-weighted (T1W), T2W, restricted diffusion on diffusion weighted imaging (DWI), and dynamic contrast enhanced (DCE) sequences with the patient in the supine position, as reported in [26]. In particular, the T2W images were acquired using a 2D fast recovery fast spin echo (FRFSE) sequence with the following parameters: repetition time (TR) 3083 ms, echo time (TE) 106 ms, field of view (FOV) 160 mm, matrix 384×224, slice thickness 3 mm, pixel spacing 0.3 mm, and later registered to intra-procedural images for planning. For all images, the patient was imaged in the supine position.

Biopsy procedure

All biopsy procedures were conducted in a 3T wide-bore MRI scanner (MAGNETOM Verio 3T, Siemens AG, Erlangen, Germany). The procedural setup in the scanner was identical to the procedure used in previous studies, such as that reported by Tokuda et al. (30). The patient was placed feet-first into the scanner in the supine position. The patient's head remained outside of the scanner. The anesthesiologist was positioned next to the patient at the head of the scanner and monitored and communicated with the patient if necessary. The patient was placed under conscious sedation and given local anesthesia to the perineum at the start of the procedure. The radiologist was positioned at the back end of the scanner and performed the biopsy. At the back end of the scanner, the tabletop was specially fitted with a special plastic baseboard, which had holes to allow attachment of leg supports, a Z-frame for calibration and the robotic needle guide device. The leg supports attached into the baseboard and were used to keep the legs raised and apart so the radiologist had access to the perineum. The table was 91 cm off the floor and the patient's perineum was positioned to be 76 cm above the tabletop.

The template, either manual or robotic, was attached to the gantry table of the scanner and registered to the MRI coordinate system using a Z-frame attached to the templates imaged by an axial volume interpolated gradient echo (Ax VIBE) images. (TR/TE = 12/2; acquisition matrix = 256 x 256; flip angle = 45°; field of view = 160 x

160m²; slice thickness = 2mm; receiver bandwidth =399 Hz/pixel). Figure 1 illustrates the patient setup as well as both templates in position. The suspicious targets identified in the pre-procedural images are re-identified in intra-procedural T2W images obtained using a combination of Body Matrix (anteriorly placed) and Spine surface (posteriorly located) coil elements (Siemens Medical Systems, Erlangen, Germany). Specifically, this intra-procedural T2W images were taken by turbo spin echo (TSE) sequence (TR/TE 5250/100 ms, FOV 140 mm, matrix 320×224, slice thickness 3 mm, pixel spacing 0.4 mm). The image registration of the pre-procedural and this intra-procedural T2W image were performed to further facilitate this re-identification of the suspicious targets (31).

The Z-frame used for calibration was a 60 mm³ cube with seven tubes of 7.5 mm diameter arranged along the outer surfaces in the shape of a Z. The tubes were filled with a contrast agent (MR Spots, Beekley, Bristol, CT), which showed as a hyper intensity on the MR images. The level of intensity of the circular cross sections of these tubes was measured and areas of hyper intensity were used to create a grid of dots. This grid was then matched to the MRI coordinate system. This process essentially allowed the robot's coordinates to be matched to those of the MR scanner. Once this calibration has occurred, the patient's anatomy on MR scan can be mapped to the robot's coordinates and the robot can be guided to any needle position by selecting the corresponding location from the patient's imaging. Complications documented up to the time of discharge were collected from the medical record.

Manual technique:

The manual approach used a manual needle guidance template which was an acrylic block that was 100 x 120 x 125 mm³ and had a grid of holes 1.3 mm in diameter spaced 5 mm apart. The template was affixed to the baseboard between the patient's legs and flush against the patient's perineum. The template had an adjustable holder, which allowed it to move along the cranial-caudal or anterior-posterior axes. However, the template could not be moved to any oblique angle. The Z-frame was attached to the template and a series of calibration images were taken, as described above. After

calibration, the Z-frame was detached from the template.

The target location was determined by taking an initial MR image after the template was in place. For each core sample collection, the clinician used a planning and navigation software, 3D Slicer, to plan which guide hole to use for biopsy needle insertion and how deep to insert the needle. 3D slicer accessed the MR images stored on the BWH network using the Digital Imaging and Communications in Medicine (DICOM) program. The program allowed the clinician to view the images with various filters to plan his procedure. The clinician inserted an 18-gauge x 15cm MRI compatible needle through the hole and took a confirmation image using axial 2D multislice Turbo Spin Echo images (TR/TE = 2700 ms/106 ms; acquisition matrix = 280×280 ; flip angle = 48° ; field of view = $200 \times 200 \text{ mm}^2$; slice thickness = 3 mm; receiver bandwidth = 252 Hz/pixel; imaging time: approx. 1 min). If the needle was too far from the target, the clinician removed and reinserted it. Confirmation images were taken after each insertion. When the clinician felt the needle was acceptably close to the target, a core sample was taken. This was repeated multiple times for each target as directed by the clinician's judgment. There were also multiple targets selected for some patients.

Robotic technique:

The robotic approach used a motorized template made of polyetherimide, aluminum alloys and brass alloys. It consisted of a frame with two crossbars that intersected at a 90-degree angle (Figure 2A). The frame was connected to a box containing the ultrasonic motors that power the device. Each motor powered one of the two crossbars. The biopsy gun was positioned at the intersection point of the crossbars. A limit switch was placed at the end of each crossbar's range to provide feedback when the crossbar reached the limit of its range. The location of these switches also marked the starting position of the crossbars at the initiation of each use of the robot. The robot had the ability to set the needle insertion hole with a control resolution of 0.001 mm.

The patient was placed supine in the MRI scanner with feet facing out of the scanner. The robotic template was placed in contact with the patient's perineum and affixed to the table with screws. 3D Slicer software was also used to control the motorized template and orient the needle hole to best aim the target. An axial T2

weighted MR image was taken after the needle was aligned to the target. If further adjustment was needed, the software was used to guide the robot in adjusting needle position. Confirmation MR images were taken after each adjustment. All images from procedures were maintained on a workstation in DICOM standard format for further analysis. When the clinician felt the needle was acceptably close to the target, a core sample was taken. The key difference between the robotic and manual approaches is the process of adjusting the needle position. The manual approach relies on clinician judgment to select the best guide hole for needle insertion. The robotic template was fiducially registered to the MR scanner so the correct angle and insertion point was computed.

The 3D Slicer navigation system was used to guide both manual and robotic procedures. 3D Slicer is an open-source navigation software that was customized for use with the prostate biopsy robot (24). MR images are stored on the BWH network. 3D Slicer was able to register the robot to the MR scanner by accessing the MR images using DICOM and simultaneously communicating with the robot's controller using the OpenIGTLink program.

Measurement items

1) Accuracy

Accuracy was defined as the in plane distance between the (x,y) coordinated of the target location and the (x,y) coordinates of the needle tip as visualized on images. A log was kept for each procedure containing the following data: (1) needle hole position for the initial attempt at target, (2) adjusted needle hole position for succeeding sampling attempts (3) time of each image set, (4) time of each sample collection. The MR image taken before each sample collection was reviewed. These images were identified by time stamp, which was matched to the time stamp of each collected sample. The selected target coordinates were recorded at the start of each case. The needle artifact was identified on each image. The distance between the target coordinates and the needle artifact at the level of the needle tip was measured. Cases were not used if a needle artifact could not be identified in the image series. We gathered data for every needle positioning attempt, including those that resulted in further adjustment rather

than sample collection. The z coordinate of the needle position was determined by the radiologist and was not included in the accuracy assessment.

Inserting a needle into the prostate can cause two changes: displacement and deformation. We took measures to minimize the impact of each of these on our results. The prostate can become slightly displaced after a needle insertion so that the target would no longer be in the exact coordinates that it started. For this reason, the target location was re-acquired after each sampling attempt by matching the suspicious lesions identified on pre-operative imaging to the needle guide coordinates. In addition to displacement, multiple needle punctures into the prostate can deform the prostate or change its tissue structure. This change is harder to correct on subsequent attempts. To minimize the error introduced by this phenomenon, we collected accuracy data from the first target in each case only.

Images were reviewed to identify the in-plane distance between the target location and needle tip position. Target location was acquired from the logs from the procedure. Multi-planar reconstruction view in the DICOM PACS workstation (aycan OsiriX pro, Rochester, NY) was used to identify the needle artifact in each image. The right-left and anterior-posterior coordinates of tip of the needle artifact were recorded. These coordinates and the coordinates of the target were used to find the distance between the two points.

The average distance from the target over all attempts was measured, as well as the best attempt for each case. The best attempt used the coordinates of the needle tip closest to hitting the target. The latter measure is reported because the clinician usually made multiple adjustments to the needle hole before taking a sample so the closest distance to the target represents the point where sampling actually occurred.

2) Time

We compared procedure time between the robotic and manual approaches. Two kinds of procedure time were recorded for this comparison. First, “core” procedure time was defined as the time between the registration image scan and the final image scan; this represents the procedure time not including the time taken to transport the patient, start anesthesia and set up equipment. These data were retrieved from the image

header information stored in the images in DICOM standard format. The second time measurement was “whole” procedure time, which was retrieved from the logbook in the operating rooms. The “whole” procedure time was defined as the time between when the patient entered the MRI scanner room and when they left the scanner room. Induction of anesthesia, placement of the patients in the stir-ups, placement of MRI, preparation of perineum sites, “core” procedure, and ending of anesthesia are all included in the “whole” procedure time.

3) Pathology

Biopsy cores were fixed in formalin and processed according to standard protocol for prostate biopsy. The cancer diagnosis for each core sample was recorded. In cases where cores were positive for cancer, the percentage of cancer volume in the positive core was recorded. If multiple cores returned positive for a patient, the percentages were averaged into a single value.

Statistical analysis

All outcome parameter distributions were tested for normality using skewness/kurtosis test for normality and histograms. Log-transformation was applied to outcome parameters that exhibited significant skewness, and the transformed parameter distributions were confirmed for normality via skewness/kurtosis test. In this study, skewness was found in accuracy measurements and procedure time and these values were therefore log-transformed for further analysis. All numbers reported hereafter for accuracy and procedure time are log-transformed values, which were transformed backward after skewness of data distribution was corrected by log transform to accommodate statistical analysis using the F-test and t-test, as described below. An alternative option was to use a non-parametric test, such as a Kruskal-Wallis test, to avoid the requirement that the samples be normally distributed. However, this would still assume that the samples had equal variances. Each method had drawbacks and the log transformation was chosen because it allowed normalization of data with a single manipulation.

Similarity of variances was confirmed using the F-test for difference in variance, and a two-sample t-test with unequal variance was employed for each pair that had significantly different variance. Two-sample t-tests were applied to compare each measurement item in manual and robotic procedures. In addition, we conducted adjusted analyses for each outcome measure using a multiple regression model method, adjusting for age, PSA, and volume of prostate. We adjusted for age and PSA to ensure that the patient populations studied were equivalent on basic characteristics.

All tests were conducted in Stata version 11 at an alpha level of 0.05, and only two-sided p-values were reported.

Section 3: Results

Patients

Ninety-seven patients underwent 99 procedures. Fifty-six procedures performed between December 2009 and October 2013 used the manual template. Four of these fifty-six were converted from robotic to manual due to technical difficulties in October 2013. Forty-three procedures between September 2012 and October 2013 were performed using the robotic needle-guidance template. Technical difficulty included malfunction of optical motion limiter at one of the axis and slippage of screw drive.

The mean age of the patients was 66.01 (± 6.81) years (range: 48-81 years), median prostate-specific antigen level of 8.50 ng/mL (range: 0.02 –86.70 ng/mL) and median prostatic volume of 42.75 cc (range: 10.3 – 177.0 cc). Patient characteristics are summarized in Table 1.

Measurement results

1) Accuracy

We collected data on accuracy from every needle positioning attempt, including those that resulted in further adjustment rather than sample collection. This was so we could see if every needle positioning attempt was different between the two groups or only the most adjusted one.

Data for image based accuracy analysis was available for 88 cases (47 manual, 41 robotic) (Table 2). Log-transformation of average distance and best distance from the target was compared between the two approaches. The difference in their log of average distance from all needle placement attempts was not statistically significant ($p < 0.20$) even after adjusting for the confounders ($p < 0.30$), at a study power of 17%. However, there was significant statistical difference in the log of accuracy for the best attempts of needle placement only; robotic approach 2.39 (± 0.97) had statistically higher accuracy than manual approach 3.71 (± 0.86) by $p < 0.027$. This difference remained significant even after adjusting for the confounders ($p < 0.032$) at a statistical study power of 61%. Figure 3 illustrates this phenomenon with a representative case for the manual and robotic groups. The initial attempt in each case was approximately the same distance away from the target (3.9 mm vs. 3.1 mm). However, the second and

third attempts with the robot came progressively closer to the target while subsequent attempts with the manual template remained the same distance away.

2) Time

The mean core procedure time for the robotic group was 90.82($\pm$ 15.93) minutes, compared to 100.63($\pm$ 26.24) minutes for the manual group. The whole procedure time was 141.67($\pm$ 19.47) for the robotic group and 151.29($\pm$ 37.88) minutes for manual group. The core procedure time was statistically significantly shorter in robotic approach ($p < 0.030$); the whole procedure time was not statistically significantly different ($p < 0.14$) between robotic and manual group.

3) Pathology

The histopathologic outcomes are summarized in Table 3. A diagnosis of cancer was confirmed in 30 of 56 cases in the manual group (53.57%) and 25 of 42 cases in the robotic group (59.52%). Further pathologic analysis was done with all cores that returned positive for tumor. This included 147 of the 541 cores (32.16%) taken from patients in the manual group and 137 of the 310 cores (44.19%) taken from the robotic group ($\chi^2 p = 0.018$). Fraction of positive cores was also compared between robotic and manual approaches. This showed a significant difference ($p < 0.018$) after adjusting for potential confounders: volume of prostate, PSA and age.

Complications

Six patients in the manual group had procedure-related complications – 5 had hematuria, 1 had urinary retention and 1 had a hematoma on the scrotum and thighs. One patient in the robotic group experienced urinary retention.

Section 4: Conclusions and future work

Conclusions

In this study, we demonstrated the utility of a robotic needle-guidance template device as compared to a manual template for in-bore 3T transperineal MR guided prostate biopsy. Our study involving 97 patients and 99 cases has shown that that robotic needle-guidance template provided a better sampling accuracy than manual template, higher fraction volume of positive tissues in core samples, and reduced core procedure time. Diagnostic yield were similar between the two groups.

Our study is in accordance with previous work on MRI-guided robotics for prostate biopsy. Previous work on robotic biopsy devices has shown average targeting accuracy to range between 2.5 mm (17) and 5.7 mm (13) in raw value. Our mean targeting error in log transformed value of 5.42 mm falls within this range. One of the benefits of using MRI guidance is that the clinician can use intraoperative images to not only to see the target but also to adjust the needle position (24). For this reason, the needle placement accuracy test in our study included both measurements from all needle placements to a target, as well the best attempt where the needed reached closest to the target. The best attempt was often after multiple needle insertion attempts and image-based assessment of accuracy of needle placements. We found that accuracy improved with subsequent needle placement attempts for the robot to a greater extent than it did for the manual template (3.86 mm for the robot vs. 2.80 mm for manual in log transformed value). This indicates that the robot is better able to help the clinician fine-tune the needle position. The manual template, on the other hand, consists of a grid of holes that are 5 mm apart and therefore does not allow the same level of specificity in its adjustment. Regardless, even the manual template had an average accuracy of 5.75 mm, which is comparable to the range reported in literature (13,17).

We also measured procedure time in two different ways to see if use of the robot cut down the procedure time. The data for time was log transformed to make it easier to interpret because it was highly skewed in raw form. We found that the “core” procedure time was shorter in the robotic group (90.82 min vs. 100.63 min; $p < 0.030$). The “core” time was the time spent in the biopsy procedure, not including pre- and post- operative periods. The “whole” procedure time, including setup was comparable in both groups

(141.67 min vs. 151.29 min; $p < 0.14$).

We compared the pathology results from both groups to see if this gain in accuracy was reflected in the rate of diagnosis or profile of cores taken. The diagnostic rate from the robotic procedure was 59.52%, which is on the high end of published values for MRI-guided biopsy, which range from 51-59% (2,6). This is comparable to the published yield of 54% from a transrectal robotic device designed by Yakar et al (15). The rate of diagnosis in the manual group was also within this range, at 53.57%.

We further analyzed the percent cancer volume to see if the improvement in accuracy changed the profile of the cores taken. Previous studies have shown that the volume of cancer found in the biopsy sample is useful in predicting the outcome of therapy (33, 34). Our pathology results indicate that biopsy sampling with the robot results in cores with the same percent cancer volume as the manual template.

Our study was a retrospective cohort study. While some of the data collection was prospective, the study maintains the limitations of a retrospective study. Because the study relied on data that had already been collected, it was not possible to evaluate additional confounding factors or add additional variables to the analysis.

This study is the first to present quantitative comparative analysis of accuracy for an MRI-guided prostate biopsy robot. The robot was found to be superior to the manual template in accuracy, core procedure time and diagnostic yield. This suggests it is a realistic contender for more widespread use in prostate biopsy cases going forward.

Limitations

Our study has some limitations. First, the sample size was large enough to do some quantitative analysis of accuracy. However, a larger sample size would allow us to do a more thorough accuracy analysis and evaluate more of our variables for statistical significance. The data suggest a learning curve for doing MRI-guided biopsy; the earliest cases had lower image quality and took more time than those that came later. We did not separate these early cases in our data set. Finally, some of the cases had poor MR image quality and we were unable to identify a needle artifact from these. We were forced to exclude these cases from accuracy analysis, which decreased our functional sample size. Unfortunately, it is a natural phenomenon that professionals

become more experienced in their work over time so that no matter when the procedures were divided, there would be some element of natural improvement in the biopsy procedure. This is particularly true for the robotic template, which was a new device that the clinician had not used before. The manual method, on the other hand, was a technique with which the clinician was already familiar at the start of the study.

A corollary of this is the suspected learning curve of the diagnostic radiologists in evaluating which lesions were suspicious. This is particularly notable in the setting of identifying MR suspicious prostate lesions. During the study period, which lasted from 2009-2013, there were updates to the way prostate cancer is identified on imaging, with the introduction of the PI-RADS system which provided clinical guidelines for the use and interpretation of multi-parametric MRI for prostate cancer diagnosis (36). The introduction of these guidelines potentially changed the way the radiologists used and interpreted MR in the setting of prostate cancer.

Finally, as described above, this was a retrospective study and as such is subject to the limitations of the methodology. Specifically, the study was limited to data that had already been collected, including which potential confounders had been investigated.

Future work

This study had a number of limitations, as described above, which suggest options for future work. Firstly, using an even larger sample size in a prospective fashion would allow us to do a more thorough quantitative analysis of all of our investigative variables. Secondly, a repeat analysis would be useful once the clinician has more experience using the device as this may change the amount of time it takes to setup the device or plan the procedure using the software developed specifically for the robot. In this study, we found that while the time spent in procedure was shorter for the robotic device, the total procedure time was comparable, due to the relatively longer time spent in setting up the robot. This phenomenon may disappear with time and experience.

More broadly, this robotic design could be more applied to other types of procedures. Currently, the robot is designed only to perform prostate biopsies. However, many other types of procedures require needle deployment with fine precision and

accuracy. This includes procedures like focal transperineal radiotherapy (9) or cryoablation (35) to destroy tumor tissue. A robotic device that could be widely applied to numerous types of procedures would be a useful tool for the future of minimally invasive procedures.

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Table 1. Patient characteristics

		All	Manual	Robotic
Number of patients		99	56	43
Age (y)	Mean($\pm$ SD)	66.01($\pm$ 6.81)	66.91($\pm$ 6.50)	64.84($\pm$ 7.09)
	Range	48.00-81.00	50.00-81.00	48.00-78.00
PSA (ng/mL)	Median	8.50	8.55	8.40
	Range	0.02-86.70	1.69-48.78	0.02-86.70
Prostatic volume (cc)*	Median	42.75	47.85	38.00
	Range	10.30-177.00	11.0-177.00	10.30-107.65

*Data is reported for 83 patients – 49 manual, 34 robotic

Table 2a: Accuracies and procedure time (raw data)

		All	Manual	Robotic
Average distance (mm) *	Median	5.57	5.76	5.39
	Range	1.48 - 26.78	1.48 - 26.78	1.94-26.27
Best distance (mm) *	Median	3.14	3.86	2.80
	Range	0.07-24.18	0.55 - 24.18	0.07-23.68
Core Procedure time (minutes) **	Mean ($\pm$ SD)	96.33 ($\pm$ 22.74)	100.63 ($\pm$ 26.24)	90.82 ($\pm$ 15.93)
	Range	48.47 - 181.18	48.47 - 181.18	63.08 - 135.93
Whole Procedure time (minutes) *	Mean ($\pm$ SD)	147.12 ($\pm$ 31.50)	151.29 ($\pm$ 37.88)	141.67 ($\pm$ 19.47)
	Range	91-248	91-248	108-186

*Data is reported for 88 patients – 47 manual, 41 robotic

**Data is reported for 98 patients – 55 manual, 43 robotic

Table 2b: Procedure time and accuracies (after skewness correction by log-transformation)

		All	Manual	Robotic	p-value	Adjusted p-value
Average distance [Log $\pm$SD] (mm)	Mean	5.75 [1.75 $\pm$ 0.52]	6.05 [1.80 $\pm$ 0.55]	5.42 [1.69 $\pm$ 0.48]	0.20	0.30
	($\pm$ SD)	(3.42, 9.68)	(3.49, 10.49)	(3.35, 8.76)	Power	= 17%
Best distance [Log $\pm$SD] (mm)	Mean	3.03 [1.11 $\pm$ 0.94]	3.71 [1.31 $\pm$ 0.86]	2.39 [0.87 $\pm$ 0.97]	0.027	0.032
	($\pm$ SD)	(1.19, 7.77)	(1.57, 8.76)	(0.90, 6.30)	Power	= 61%
Whole Procedure Time (minutes)	Mean ($\pm$ SD)	147.12 ($\pm$ 31.50)	151.29 ($\pm$ 37.88)	141.67 ($\pm$ 19.47)	0.14	0.40
Core Procedure time (minutes)	Mean ($\pm$ SD)	96.33 ($\pm$ 22.74)	100.63 ($\pm$ 26.24)	90.82 ($\pm$ 15.93)	0.030 Power	0.323 = 62%

Table 3: Histopathology

	Total	Manual	Robotic	p-value	Adjusted p-value
Cancer yield by Patient (positive cases/total)	55 /98	30/56	25/42	0.557	0.367
Ratio (%)	56.12	53.57	59.52		
Cancer Yield by Samples (positive samples/total)	311/851	174/541	137/310	0.627	0.018
Ratio (%)	36.54	32.16	44.19		
Positive fraction: Mean (SD)	0.35 (0.26)	0.42 (0.25)	0.26 (0.24)	0.001	0.011

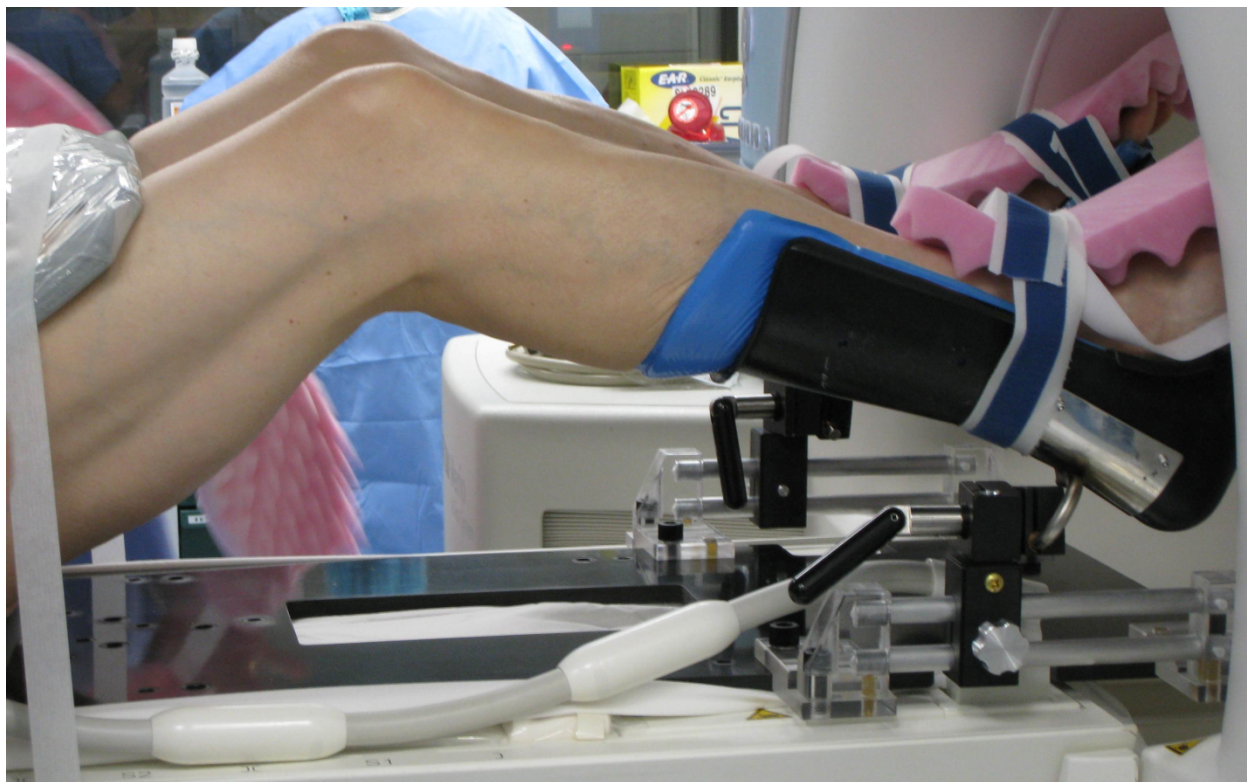
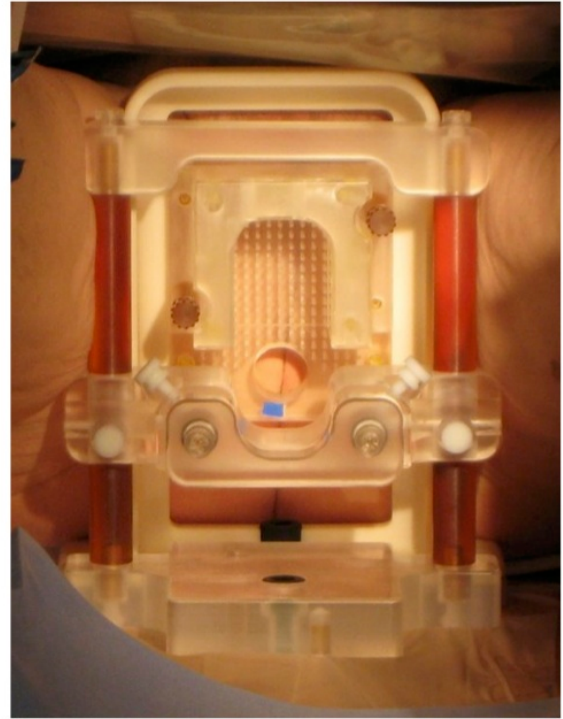


Figure 1: Apparatus setting in in-bore MRI-guided transperineal prostate biopsy. Stirrups (1) are placed on a patient board (2) placed on the table. The robotic needle-guidance template (3) is screwed on to the patient board after patient is placed on the patient board and preparation at perineum site is performed. An abdominal surface coil (4) is over the patient pelvis and the robotic template.

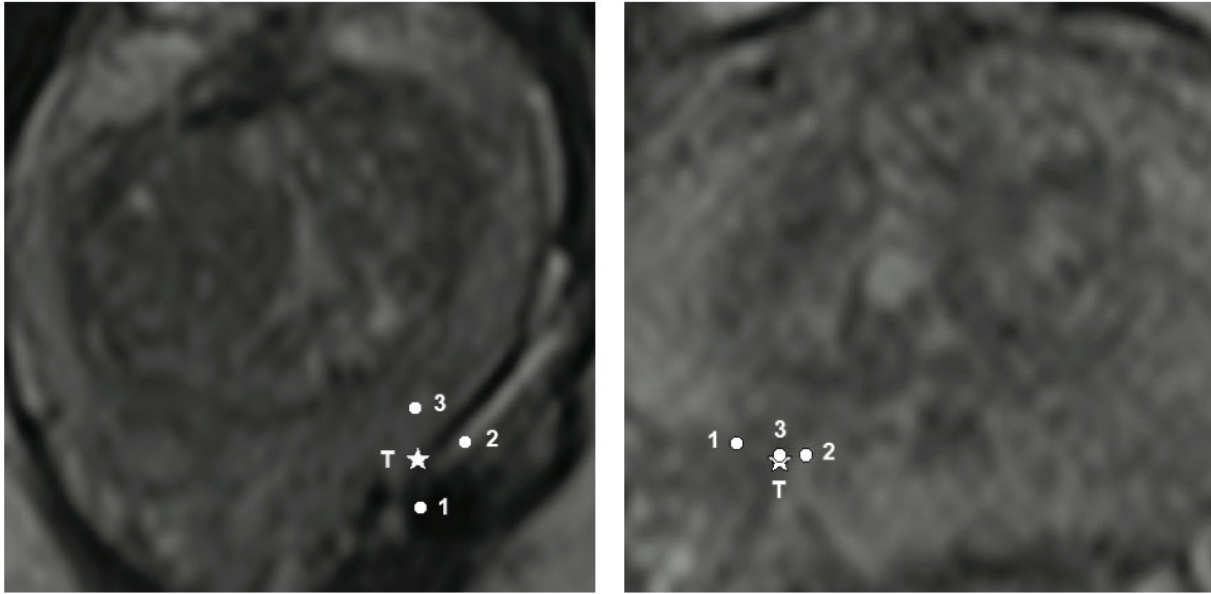


A.



B.

Figure 2: Comparison of robotic template (A) and manual needle-guidance template (B). Both templates are positioned at the patient's perineum and attached to the tables with screws.



A.

B.

Figure 3: Magnified views of prostate gland using axial T2-weighted turbo spin-echo MR image. White star indicates target and white circles represent needle positioning attempts, number 1 through 3 chronologically. (A) In the manual procedure, subsequent needle positioning attempts do not get closer to the target. Distance from the target is 3.9 mm, 4.0 mm, and 4.00 mm respectively. (B) In the robotic procedure, needle positioning attempts get progressively closer to the target. Attempts are 3.1 mm, 1.9 mm and 1.0 mm away from the target.