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Targeted augmented reality-guided transperineal prostate biopsies study: initial experience

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Abstract

Background: Transperineal biopsy of magnetic resonance imaging (MRI)-detected prostate lesions is now the established technique used in prostate cancer (CaP) diagnostics. Virtual Surgery Intelligence (VSI) Holomedicine by Apoqlar (Hamburg, Germany) is a mixed reality (MR)/augmented reality (AR) software platform that runs on the HoloLens II system (Microsoft, Redford, USA). Multiparametric prostate MRI images were converted into 3D holograms and added into a MR space, enabling visualization of a 3D hologram and image-assisted prostate biopsy.

Objective: The Targeted Augmented Reality-GuidEd Transperineal (TARGET) study investigated the feasibility of performing AR-guided prostate biopsies in a MR framework, using the VSI platform in patients with MRI-detected prostate lesions.

Methods: Ten patients with a clinical suspicion of CaP on MRI (Prostate Imaging-Reporting and Data System, PI-RADS 4/5) were uploaded to the VSI HoloLens system. Two MR/AR-guided prostate biopsies were then acquired using the PrecisionPoint Freehand transperineal biopsy system. Cognitive fusion biopsies were performed as standard of care following the MR/AR-guided prostate biopsies.

Results: All 10 patients successfully underwent MR/AR-guided prostate biopsy after 3D MR images were overlaid on the patient's body. Prostatic tissue was obtained in all MR/AR-guided specimens. Seven patients (70%) had matching histology in both the standard and MR/AR-guided biopsies. The remaining three had ISUP (International Society of Urological Pathology) Grade 2 CaP. There were no immediate complications.

Conclusion: We believe this is a world first. The initial feasibility data from the TARGET study demonstrated that an MR/AR-guided prostate biopsy utilizing the VSI Holomedicine system is a viable option in CaP diagnostics. The next stage in development is to combine AR images with real-time needle insertion and to provide further data to formally appraise the sensitivity and specificity of the technique.

Keywords: diagnostic, HoloLens, prostate cancer, transperineal biopsy, virtual reality

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Introduction

Prostate cancer (CaP) is the most common form of cancer in men in the UK, with over 52,000 new cases diagnosed each year and projections predicting further rises in the next decade.[1,2] The mainstay diagnostic investigation for CaP is an MRI-targeted prostate biopsy. Increasingly this is performed through the transperineal route, as advocated by the European Association of Urology, because of its higher accuracy, reduced risk of sepsis due to faecal contamination and less need for antibiotic prophylaxis, on a background of a global rise in antimicrobial resistance rates.[3–7]

The role of multiparametric magnetic resonance imaging (mpMRI) in the diagnostic pathway for CaP has been significant over the past decade. The PROMIS (Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer). Trial confirmed an mpMRI is a highly sensitive test (93%) for the detection of clinically significant CaP (csCaP), with MRI-targeted prostate biopsies increasing overall accuracy rates in detection of clinical significant cancers by 18%.[8] Despite this, current biopsy techniques are associated with suboptimal diagnostic accuracy, with up to 22.8% of men with initial negative biopsies subsequently were diagnosed with csCaP following repeat biopsies.[9]

With the rapid advancement of artificial intelligence (AI), virtual, augmented (AR) and mixed reality (MR) are being increasingly investigated for its application and utilization in medical science and education. There has been a great emphasis already in training and education, and pre-operative surgical planning in Urology and Orthopaedics[10–12] and bear the potential to further increase efficiency in healthcare and enhance patient care.

Virtual Surgery Intelligence (VSI) Holomedicine by Apoqlar is an MR/AR software platform that runs on the HoloLens II system (Microsoft). The platform allows MRI and Computed Tomography (CT) imaging to be uploaded and viewed in AR. The VSI creates a 3D hologram from the mpMRI dicom data. The hologram can be manipulated and overlayed onto the patient. This provides an MR experience in which the hologram is used to target the prostate tumour.

The Targeted Augmented Reality-GuidEd Transperineal (TARGET) study combined an MR VSI platform to assist in performing a free-hand cognitively targeted transperineal prostate biopsy and investigated the feasibility of applying this novel technique in patients with MRI-detected lesions, utilizing the HoloLens II system to project a 3D MRI image of the prostate with the lesions highlighted to help guide the cognitive targeting of the lesions by the operating surgeon.

Methods

The TARGET study is a prospective, single-centre study, conducted at Royal Berkshire Hospital with the primary objective to assess the feasibility of MR/AR-guided prostate biopsy as a viable option in CaP diagnostics.

Between June 2022 and January 2023, 10 patients with a suspicion of clinically significant CaP on mpMRI (Prostate Imaging-Reporting and Data System, PI-RADS 4/5) were recruited to the study. All patients provided formal written consent prior to enrolment.

The study received funding from the Joint Academic Board, University of Reading and Royal Berkshire Hospital Research Department and ethical approval from the NHS West Midlands Solihull Research Ethics Committee (REC ref: 20/WM/0249) [IRAS ID: 282488]. Funding was received for 10 patients to be recruited to the study.

Cancer detection

All patients underwent mpMRI at 3 Tesla magnetic field strength. Standardized sequences were used (axial T1/T2, sagittal T2, coronal T2, diffusion and gadolinium-enhanced sequences).

The resultant images were assessed by a consultant radiologist. The PI-RADS (v2.1) was used to quantify the probability of csCaP.[13] A score of 1 indicated a low chance of significant disease, whereas a score of 5 indicated a high probability of significant disease.

Patients with PI-RADS lesions 4 and 5 were included in the current study. PI-RADS 3 lesions were excluded for the purpose of this pilot study, due to the lower probability of underlying CaP in these patients. In a previous meta-analysis study by Oerther *et al.*,[14] rates of csCaP with PI-RADS 3 lesions were reported to be 20%. In contrast, PI-RADS 4 and 5 detected up to 59% and 85% of csCaP, respectively. As such, in keeping with the primary objective of this study, only PI-RADS 4 and 5 were included in the study.

Data transfer

Axial T2-weighted sequences and ADC sequences from diffusion weighted imaging were used to create Holograms using the VSI platform. Anonymized dicom data was uploaded to the VSI cloud and the Apoqlar software created the 3D Hologram that was transferred to the HoloLens II device.

HoloLens

Developed by Microsoft and first announced in 2015, HoloLens is an AR headset. By overlaying

virtual objects and holograms onto the real world, HoloLens allows users to interact with them.

The HoloLens headset consists of transparent lenses that project holographic images onto the wearer's field of view (MR environment). The device utilizes various sensors, including cameras, depth sensors and an inertial measurement unit, to detect, assess and understand the user's surroundings and track their movements.

The HoloLens platform allows developers to create software to utilize this technology and incorporate features including spatial mapping and gesture recognition to provide an MR interface.

Procedure and biopsy protocol

All biopsies were performed by a single consultant urologist with over 15 years' experience in prostate biopsies. All patients were placed in the lithotomy position under general anaesthetics.

A transrectal ultrasound probe (BK Medical, Burlington, US) was first used to obtain a US scan of the prostate. The HoloLens headset was then worn by the operating surgeon and a preuploaded 3D hologram of the prostate from the mpMRI was then projected within the field of view with regions of interest highlighted. Through hand gestures, the operating surgeon was able to interact and rotate this 3D image.

After confirming the regions of interest on the mpMRI, cognitively targeted prostate biopsies were performed using the freehand PrecisionPoint transperineal biopsy system, with at least two cores in each target lesion. The HoloLens device was then removed, and a standard freehand PrecisionPoint transperineal prostate biopsy was performed following the Ginsberg protocol.[15]

Results

Demographics and pre-interventional details

A total of 10 patients were recruited into the TARGET study. The patients had a median age of 62 years [interquartile range (IQR): 52.5–63] and the median prostate specific antigen (PSA) at presentation was 8 ng/ml prior to having a mpMRI of the prostate (Table 1). Six patients had a mpMRI demonstrating PI-RADS 4 lesions, and the remaining patients showed PI-RADS 5 lesions.

Table 1. Patient age and PSA.

Patient factor	Median (IQR)
Age (years)	62 (52.5–63)
PSA (ng/ml)	8 (4.5–13.25)
Prostate volume (ml)	38.5 (32.25–53.5)
PSA density	0.24 (0.13–0.43)

IQR, interquartile range.

Histological analysis

Prostatic tissue was obtained in all MR/AR-guided target specimens. The standard Trans Perineal (TP) biopsy showed that five patients had histological confirmation of CaP. Three of these patients had ISUP Grade 2 CaP, one had ISUP Grade 4 CaP and one had ISUP Grade 5 CaP. Three patients had benign prostatic tissue and two patients had histological findings consistent with prostatitis.

The MR/AR-guided biopsies detected the highest-grade disease in two patients (40%) of the five patients with underlying CaP. Of the patients with underlying ISUP Grade $\geqslant$3 disease, the MR/AR-guided target biopsies were positive for the predominant cancer in all the cores taken (100%). Three patients had specimens, which showed benign histology with the MR/AR-guided target biopsy, whilst the standard biopsy demonstrated ISUP Grade 2 (Gleason 3 + 4) CaP (Table 2).

The median operating time was 13 min (IQR: 12–16), which included the set up and use of the HoloLens II headset. In the month preceding, the median operating time for 'standard' transperineal biopsies was 12 min (IQR: 11–13). All patients were discharged the same day after successfully voiding. There were no immediate Clavien–Dindo complications within this cohort or within the subsequent 28 days post-biopsy. All five patients diagnosed with csCaP underwent radical treatment. Two patients underwent radical prostatectomy and three were treated with radical radiotherapy (Table 3).

We further analysed the correlation between the histology results of the targeted biopsy and the size and locations of the PI-RADS lesion in the five patients diagnosed with CaP (Table 4). Larger PI-RADS lesion had a greater probability

Table 2. Patient biopsy results.

Patient	Standard biopsies			Target MR/AR-guided biopsies		
	Positive cores for CaP (%)	Total cores	Histology	Positive cores for CaP (%)	Total cores	Histology
Tar 01	6 (30)	20	G3 + 4 (ISUP G2)	0 (0)	2	Benign
Tar 02	0 (0)	15	Chronic prostatitis	0 (0)	2	Chronic prostatitis
Tar 03	3 (25)	12	G3 + 4 (ISUP G2)	0 (0)	2	Benign
Tar 04	0 (0)	17	Benign	0 (0)	3	Benign
Tar 05	3 (37)	8	G3 + 4 (ISUP G2)	0 (0)	2	Benign
Tar 06	6 (46)	13	G4 + 4 (ISUP G4)	2 (100)	2	G4 + 4 (ISUP G4)
Tar 07	8 (40)	20	G4 + 5 (ISUP G5)	3 (100)	3	G4 + 5 (ISUP G5)
Tar 08	0 (0)	13	Benign	0 (0)	2	Benign
Tar 09	0 (0)	14	Prostatitis	0 (0)	3	Prostatitis
Tar 10	0 (0)	14	Benign	0 (0)	3	Benign

Table 3. Patient outcomes.

Patient	Histology	Treatment
Tar 01	G3 + 4 (ISUP G2)	RARP
Tar 02	Chronic prostatitis	Treated with antibiotics and on PSA monitoring
Tar 03	G3 + 4 (ISUP G2)	Prostate brachytherapy
Tar 04	Benign	PSA monitoring
Tar 05	G3 + 4 (ISUP G2)	Radical RT
Tar 06	G4 + 4 (ISUP G4)	RARP
Tar 07	G4 + 5 (ISUP G5)	Radical RT
Tar 08	Benign	PSA monitoring
Tar 09	Prostatitis	Treated with antibiotics and on PSA monitoring
Tar 10	Benign	PSA monitoring

RARP, Robotic Radical Retropubic Prostatectomy; RT, Radiotherapy.

of positive biopsy for CaP using the MR/AR-guided biopsy.

Discussion

The primary aim of the TARGET study was to identify the feasibility of performing an MR/AR-guided TP biopsy. All 23 (100%) MR/AR-guided biopsies taken contained prostatic tissue, showing that MR/AR-guided prostate biopsies are possible and a potential viable option in CaP diagnostics.

The MR/AR-guided biopsies were able to detect CaP in only two (40%) of the five patients, though it was able to pick up tumour in all patients with underlying high-grade disease. Although there was a lesser emphasis on the diagnostic capabilities of the novel technique, we acknowledge only two of the five CaP were identified using the MR/AR-guided TP biopsy (Table 5). Whilst the technology is intuitive and no formal training is required, there is nonetheless a learning curve to the novel technique, which will improve with experience. One other factor that may have contributed to the lower diagnostic rates of CaP is the size of the PI-RADS lesion. As highlighted in Table 4, Tar 03 and Tar 05 had smaller PI-RADS lesions on MRI at 9 and 14 mm in comparison to the two patients that picked up CaP using the MR/AR-guided biopsy at 15 and 21 mm. Due to the lack of real time tracking of the needle, smaller lesions become more difficult to target accurately. However TARGET 2 (under development and detailed further below) will aim to address this issue by incorporating a software update, which allows for live needle tracking using fiducial markers to localize the prostate, and thus we expect an improvement in the accuracy and cancer detection rates going forward.

Table 4. Size and location of PI-RADS lesions with prostate cancer.

Tar	Location of PI-RADS lesion	Size of PI-RADS lesion (mm)	Standard biopsy	MR/AR-guided biopsy
1	Left PZ (base)	18	G3 + 4 (ISUP G2)	Benign
3	Left PZ (towards apex)	9	G3 + 4 (ISUP G2)	Benign
5	Right PZ (towards apex)	14	G3 + 4 (ISUP G2)	Benign
6	Right anterior (towards apex)	15	G4 + 4 (ISUP G4)	G4 + 4 (ISUP G4)
7	Left apex	21	G4 + 5 (ISUP G5)	G4 + 5 (ISUP G5)

AR, augmented reality; MR, mixed reality; PI-RADS, Prostate Imaging-Reporting and Data System; PZ, Peripheral Zone.

A similar outcome was found in transrectal cognitive fusion biopsies previously. Sparwasser *et al.*[16] examined the feasibility of using AR-guided transrectal ultrasound for prostate biopsy in four patients, achieving favourable outcomes. The study involved the utilization of Vuzix BladeR smart glasses, which displayed 2D images of the mpMRI. During the cognitive target biopsy, the user mentally aligned the real-time transrectal ultrasound with the AR displayed mpMRI images to guide the procedure effectively, and had a cancer detection rate of 46% in the AR-guided biopsies compared to 27% in the standard 12 core transrectal systematic biopsy.

We further analysed the safety and efficacy of this novel technique. The findings indicate that MR/AR-guided biopsies can be conducted safely without any major or minor complications and minimal impact on operating times. This implies that patient safety and care can be improved without placing a substantial burden on healthcare resources.

Limitation of study

There were limitations to the study that should be considered. The primary constraint is the small sample size, consisting of only 10 patients. Whilst accepting smaller sample sizes yield reduced statistical power, this TARGET study was intentionally designed as a pilot study on the feasibility of the technique, and thus 10 patients were deemed sufficient to achieve this aim. Furthermore, the diagnostic accuracy of systematic biopsies has been shown to increase the positive yield when compared to targeted biopsies alone; therefore, one would expect a lower number of positive cores to be identified in the MR/AR-guided biopsies.

Hence, additional confirmatory trials are in the process of being established, involving larger sample sizes and the inclusion of a comparative group. TARGET 2 aims to provide further assessment of the efficacy of this innovative intervention as well as improve accuracy with software updates and fiducial markers.

Modification for TARGET 2

Whilst the TARGET study has demonstrated that MR/AR-guided TP biopsy is potentially a viable option in CaP diagnostics, it is also important to recognize improvements to the technique needs to be implemented to further increase the accuracy. The current technique applied in the study enabled the surgeon to visualize the anatomy using a 3D hologram interphase with PI-RADS lesions highlighted, before proceeding with the biopsy. However, we were unable to visualize the needle in real time. As such, smaller lesions were challenging for a target biopsy, which was evident in the study. This is especially significant if there are small volumes of high grade disease, which may be missed.

As a result, the current technique utilized in the study is not primed for routine use.

As such, to advance the study further, the next crucial step in TARGET is to integrate the MR/AR image with simultaneous real-time tracking needle, aiming to enhance our diagnostic capabilities. Currently there is an upgrade in the software to allow for needle guidance. In addition, the concurrent use of fiduciary markers and surface anatomy to fix the hologram onto the patient in real time will greatly improve accuracy. We will also aim to collect a greater number of targeted

Table 5. Size and location of PI-RADS lesions.

Tar	Location of PI-RADS lesion	Size of PI-RADS lesion	Standard biopsy	MR/AR-guided biopsy
1	Left PZ (base)	18 mm	G3 + 4 (ISUP G2)	Benign
2	Right PZ (mid gland)	15 mm	Chronic prostatitis	Chronic prostatitis
3	Left PZ (towards apex)	9 mm	G3 + 4 (ISUP G2)	Benign
4	Left PZ (base)	33 mm	Benign	Benign
5	Right PZ (towards apex)	14 mm	G3 + 4 (ISUP G2)	Benign
6	Right anterior (towards apex)	15 mm	G4 + 4 (ISUP G4)	G4 + 4 (ISUP G4)
7	Left apex	21 mm	G4 + 5 (ISUP G5)	G4 + 5 (ISUP G5)
8	All PZ of the prostate	Widespread	Benign	Benign
9	Left apex	7 mm	Prostatitis	Prostatitis
10	Right TZ (mid gland)	5 mm	Benign	Benign

AR, augmented reality; MR, mixed reality; PI-RADS, Prostate Imaging-Reporting and Data System.

cores (4–5) using the MR/AR-guided biopsy as opposed to just two cores per patient.

Future potential for integrated MR/AR

The application of real-time tracking is not a novel concept, as early as 1999, Gumprecht *et al.*[17] introduced the concept of neuro-navigation in neurosurgery, demonstrating its practicality and user-friendly nature in providing real-time tracking of surgical instruments. The potential to track the needle in real-time while performing MR/AR-guided TP biopsies in patients would be a revolutionary advancement.

In a study by Li *et al.*,[18] the application of real-time needle tracking using the HoloLens II system was evaluated and trialled on a 3D-printed pelvic phantom, resulting in minimal needle targeting errors and accurate, consistent needle placement in the model.

Studies have already demonstrated significant potential for MR/AR in Urology, particularly in training, education and surgical planning. Muangpoon *et al.*[19] used the Microsoft HoloLens I system to train participants in digital rectal examination, allowing them to visualize their fingers in real time, resulting in a realistic and useful experience.

Mu *et al.*[20] evaluated the use of AR-guided percutaneous renal access in teaching renal biopsies. Novice participants showed significant performance improvements after training with the AR simulator. This highlights the value of AR as a training tool.

Surgical planning, specifically for partial nephrectomy, has seen increased emphasis. Studies by Yoshida *et al.* and Checcucci *et al.* assessed MR surgical planning using the Microsoft HoloLens system. The studies demonstrated positive opinions, high satisfaction and better understanding of anatomy with the use of MR/AR in surgical planning.[21,22]

AR is also being studied intraoperatively in robot-assisted radical prostatectomy and robot-assisted partial nephrectomy (RAPN).[23–25] Porpiglia *et al.*[23] compared an AR system with standard ultrasound guidance during RAPN. The AR guidance improved tumour and intraparenchymal structure identification, leading to reduced complications.

AR also has the potential to augment surgical treatment options. Based upon the same technology, surgical planning in the case of focal therapy, and surgical treatment of benign prostatic hyperplasia using Aquablation and Rezum could be enhanced by AR.

Further application of AI in CaP

Much still remains to be optimized in the management of CaP. In particular, the current diagnostic pathways harbours limitations in the detection of the disease and represents a key area for further improvement.[9] The Cochrane review conducted by Drost *et al.* demonstrated up to 22.8% (95% confidence interval: 20.0–26.2%) of men with initial negative biopsies subsequently were diagnosed with csCaP following repeat biopsies. The current pathway also greatly depends on subspeciality expertise for reliable interpretation of histology slides and mpMRI of the prostate.

Although AR technology such as HoloLens seeks to improve the overall diagnostic process, it is undeniable that in the future, new radiological scans and AI technology will also play a significant role in this improvement.

Albisinni *et al.*[26] assessed the role of pre-biopsy prostate specific membrane antigen (PSMA)/positron emission tomography (PET), in the diagnostic work up. The PSMA/PET has already been identified to be a highly sensitive test in detecting biochemical recurrence of CaP (62.8% of men) following primary therapy.[27] The review concluded the PSMA/PET alone will not replace the current mpMRI pathway in the pre-biopsy setting. However, it would be a useful adjunct to mpMRI in detecting csCaP and would aid in staging of the disease.

AI and in particular machine learning in CaP diagnostics has already shown potential in earlier diagnosis and prognostic predictions for patients,[28] including when utilizing Genomic Sequencing data.[29] Various studies have shown a positive impact of AI in the interpretation of histopathology. In particular, Ström *et al.*[30] demonstrated that an AI algorithm was able to distinguish between benign and malignant disease of the prostate with an area under the curve (AUC) of 0.997 and the Gleason grading of the AI algorithm achieved a mean pairwise kappa of 0.62, which was within range of an expert histopathologist (0.60–0.73). Jiang *et al.*[31] evaluated the performance of AI algorithm for the detection of csCaP on a prostate mpMRI and reported outcomes that showed the AI system had comparable results to a junior radiologists with an AUC of 0.85.

Conclusion

The rapid development of technology and its implementation in clinical practice is greatly impacting the medical field. It provides great potential to improve our accuracy and diagnostic capabilities and enhance patient care. The TARGET study is the first in the world to utilize VSI Holomedicine platform with the HoloLens II system to perform a freehand cognitively targeted transperineal prostate biopsy and has demonstrated that this novel technique is a feasible option in the diagnostic workup of CaP.

Following on from these results, the next step in the development of TARGET is to integrate the MR/AR hologram and surgical site, with concurrent real-time tracking of the needle's insertion in order to improve the technique's precision and accuracy.

Declarations

Ethics approval and consent to participate

The study was approved by the West Midlands Solihull Research Ethics Committee (REC ref: 20/WM/0249) [IRAS ID: 282488]. Written informed consent for participation and anonymized data collection for scientific purposes was obtained from all participants included in the study.

Consent for publication

Not applicable.

Author contributions

Shenthiuiyan Theivendrampillai: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Bob Yang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

Mark Little: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Christopher Blick: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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